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ANNALS OF
INTERNAL MEDICINE

VOLUME 21 OCTOBER, 1944 NUMBER 4

RÔLES OF MEDICINE AND SURGERY IN THE MANAGEMENT OF BRONCHIECTASIS *

By JOHN ALEXANDER, M.D., *Ann Arbor, Michigan*

GREAT variability in the clinical behavior of patients with bronchiectasis and the failure of many vaunted methods of treatment have led to widespread confusion concerning the management of this prevalent disease, which is encountered from early childhood to old age and which produces an appalling aggregate amount of disability.

For many years physicians and surgeons longed for the time when the curative operation of lobectomy would be safe, hoping that this would virtually solve the difficult problem of treatment. Lobectomy is now safe but, as only about half of all bronchiectasis patients are suitable for the operation, other methods of treatment, which are necessarily only palliative, must still be used for the remaining half. It is primarily because many physicians are utterly pessimistic about the effectiveness of these other methods of treatment and because of my conviction that they can often be made effective, that this article is being presented. In the course of the article I shall also discuss those various points about bronchiectasis which continue to cause confusion with regard to the etiology, diagnosis, and the medical and surgical management of the disease.

BASIC TYPES OF BRONCHIECTASIS

From the point of view of treatment, it is obviously important that a distinction be made between (1) cases of bronchiectasis in which there is no obstruction of the larger bronchi; (2) cases in which varying degrees of obstruction of the larger bronchi exist, owing to foreign body, bronchial carcinoma or adenoma, tuberculous granulation tissue or fibrous stricture in the bronchial wall, pyogenic granulation tissue and extrabronchial pressure by enlarged lymph nodes or other tumors; (3) those relatively infrequent cases which present the characteristic symptoms of bronchiectasis but in

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From the Department of Surgery, University of Michigan.

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which no bronchiectases exist, the symptoms being due to allergic or asthmatic bronchitis, or true chronic catarrhal bronchitis. The presence or absence of bronchiectases can be determined accurately only by good bronchograms, whereas differentiation between the first and second groups mentioned in this paragraph can best be made by bronchoscopy. Although bronchograms frequently reveal even partial bronchial obstruction, they do not reveal its nature.

Causes of Bronchiectasis

The bronchial obstruction of the Group 2 cases is generally acknowledged as the primary cause of the bronchiectasis. Infection of the bronchial walls beyond the site of obstruction, varying degrees of atelectasis and, sometimes, parenchymal fibrosis are important secondary causes of the bronchial dilatations. There is as yet, however, no general agreement as to the mechanism of the development of the bronchiectases in the Group 1 cases in which, at the time of the first medical examination, the larger bronchi are unobstructed. Bronchial pneumonia (frequently secondary to measles or pertussis in childhood, or to influenza) is widely recognized as the most frequent initial lesion leading to bronchiectasis. Pulmonary abscess, chronic fibroid tuberculosis and aspiration pneumonia are infrequent precursors of the disease. Chronic abscess and tuberculosis are, however, not infrequently complicated by patches of bronchiectases. The many theories that have been advanced to explain the mechanism of the development of bronchiectasis have been described in a recent book by Lisa and Rosenblatt. The explanation that seems to me best to conform to the known facts is based upon atelectasis. This explanation has been well made in articles by Boyd, Anspach, Hughes and Simpson, and has been elaborated in an especially satisfactory way by Fleischner. Briefly, poor pulmonary ventilation, which is caused by many things, results in the stagnation of viscid secretions in the small bronchi; patchy or lobar atelectasis then occurs; the highly negative intrathoracic pressure and, particularly, the pull of inspiration are not absorbed by the inelastic atelectatic part of the lung and so are transmitted to the bronchi, which dilate. If the bronchial walls become infected as a result of the stagnation of secretions (from inadequate ventilation and swelling of the mucosa), the walls become weakened and are likely to remain dilated even after the atelectasis has disappeared.

It seems to me that the interesting experimental findings of Tannenberg and Pinner do not invalidate the theory just cited. These investigators concluded, from extensive experiments upon rabbits, that both bronchial infection and partial or complete bronchial obstruction are necessary for the development of bronchiectasis, but that atelectasis is not necessary. Their conclusions were based upon experimentally produced more or less complete obstruction of large bronchi proximal to the site of development of the bronchiectases. In man, however, there is no satisfactory evidence that the large bronchi proximal to the site of development of the bronchiectases are partially

or completely obstructed at any time, except in those relatively infrequent cases in which such obstruction occurs as a result of a foreign body, or a definite intrabronchial or extrabronchial mass. In these particular patients the factors responsible for the bronchiectases may be similar to those in Tannenberg and Pinner's experimental animals, but in the larger group of patients in whom no such proximal bronchial obstruction can be demonstrated, or assumed to have preceded the development of the bronchiectases, the causative factors are probably different.

Although congenital bronchiectasis does occur, it is relatively rare. Congenital cystic disease of the lung with secondary infection is probably more frequent than the non-cystic type of congenital bronchiectasis. A satisfactory explanation of the association of bronchiectasis, cystic disease of the pancreas and vitamin A deficiency (Andersen) and also the association of bronchiectasis, situs inversus and nasal sinusitis (Kartagener's triad) has not yet been made.

The rôle played by nasal sinusitis in the development of bronchiectasis is not clear. Watson and Kibler believe that allergy is the cause of both conditions, producing swelling of the bronchial mucosa, infection and bronchiectasis. Some clinicians believe the pus of the "postnasal drip" of sinusitis is aspirated into the bronchi, producing in turn obstruction, atelectasis, infection and bronchiectasis, whereas others believe sinusitis is secondary to bronchiectasis. Although sinusitis is theoretically more likely to have caused bronchiectasis, than bronchiectasis sinusitis, in those cases in which they exist together, it is an interesting fact that it is extremely rare for bronchiectasis to develop in hitherto uninvolved pulmonary lobes, even though the nasal sinus discharge continues unabated for months or years after good bronchograms showed the limitation of the bronchiectases to, for example, one lobe.

Apart from sinusitis as a possible cause of some cases of bronchiectasis, the bronchiectases, once established in one or more lobes, do not tend to extend to other lobes, even in the course of years. An exception to this general rule occurs when some such causative condition as a bronchial pneumonia arises in a hitherto unaffected lobe and produces a new area of bronchiectases. A sharp distinction must be made, however, between the relative rarity of a spreading of the bronchiectases and the great frequency with which associated suppurative lesions of the pulmonary parenchyma do spread in the course of recurring attacks of pneumonitis. The spreading of the suppurative parenchymal lesions usually, but not always, occurs within the lobe or lobes affected by the bronchiectasis. In spite of this pathological distinction between the bronchial and the parenchymal lesions, the deleterious effect upon the patient of extension of the parenchymal lesions tends to be greater than if the bronchiectases themselves had increased in number and extent. Extension of the suppurative parenchymal lesions in a bronchiectatic lobe probably does, however, create a few new bronchial dilatations.

Bronchiectasis with and without Associated Pneumonitis

Some cases of bronchiectasis have no associated gross pneumonitis, the roentgenograms showing no pulmonary infiltration whatever, and inspection and palpation of the affected lobe at the time of a lobectomy operation showing a soft, pink parenchyma without overlying pleural adhesions. In such cases, the surgeon might question the diagnosis of bronchiectasis in that particular lobe, if the bronchograms did not give certain evidence of the correctness of the diagnosis.

In those many cases in which suppurative pneumonitis is associated with the bronchiectases, there is great variability in the lesions and in the degree of toxicity and in other clinical manifestations. Contracting fibrous tissue with microscopic evidence of diffuse parenchymal suppuration, or gross evidence of tiny or larger parenchymal abscesses, in addition to the bronchiectases themselves, and more or less extensive pleural adhesions, are the principal lesions. Contraction of the fibrous tissue may produce areas of obstructive emphysema and cyst-like dilatations of the small bronchi, or a tension type of parenchymal abscess. Patches of emphysema and emphysema of unaffected lobes may, however, be entirely compensatory for the contraction of the affected lobe or lobes.

The cellular infiltration and the fibrous tissue in the parenchyma tend to cause the affected lobe to be firm and small. This condition is not predominantly atelectasis although, unfortunately, it is usually referred to as such, probably because the roentgenographic appearances of the two conditions are similar (including the drawing of surrounding structures toward the small lobe) and because a pure form of total lobar atelectasis (which is capable of disappearing and leaving a normal lobe) often initiates the train of events leading to bronchiectasis and a small dense fibrotic lobe (which can never again become a normal lobe). Boyd, Anspach and others have described the relationship between bronchiectasis and pure lobar atelectasis that is represented roentgenographically by a small triangular shadow.

Symptoms and Signs

The symptoms and signs of bronchiectasis are cough with or without sputum or hemoptysis; scanty or abundant purulent or mucopurulent sputum that may be intermittently foul in odor; susceptibility to frequent upper respiratory or bronchial "colds" that may be so mild as to resemble a true chronic bronchitis or so severe as to be diagnosed as pneumonia; asthma-like attacks that are not due to asthma but that respond to epinephrine or ephedrine, which relieves the bronchial mucosal congestion and, consequently, the wheezing; continuous or intermittent fever, that may be trivial in amount; fatigue that may be so great as to be disabling or so little that only the patient's family recognizes it; malaise; weakness; loss of weight; night sweats; anemia; pleurisy; dyspnea and miscellaneous other symptoms and

signs. The psychological disability that the social and economic handicaps of bronchiectasis create has been ably described by Churchill and by Riggins.

There is a surprising variability in the symptoms, as well as in their severity, in different cases of bronchiectasis, and also in the same patient at different times. In some patients the symptoms are so mild or atypical that the true diagnosis is not even suspected, the symptoms being attributed to undernourishment, a frail constitution, anemia, asthmatic bronchitis or chronic bronchitis; this is especially so in children. In other patients, recurring attacks of suppurative pneumonitis are diagnosed as pneumonia or unresolved pneumonia without the basic pathological condition being suspected. Even when the bronchiectatic lesions are not in the upper lung, tuberculosis is often mistakenly diagnosed because of the similarity in symptoms, especially when there is hemoptysis; there are many bronchiectasis patients in sanatoria in whom tubercle bacilli have never been found in the sputum and in whom good bronchograms have never been made.

Diagnosis

The diagnosis of bronchiectasis is suggested by the history, symptoms, physical signs and the roentgenographic and bronchoscopic findings. Almost without exception, however, an absolute diagnosis depends upon iodized oil bronchograms. Physical examination of the lungs yields such variable findings that its chief value is in the localization of some pulmonary abnormality. In a considerable number of cases in which there is no associated pneumonitis, there may be a complete absence of abnormal physical findings; râles and some alteration in breath sounds may be demonstrable at a subsequent examination. Patients having the parenchymal cellular infiltration and fibrosis of suppurative pneumonitis have the physical findings that such lesions produce. It is an interesting fact, however, that a thorough evacuation (by postural drainage or bronchoscopy) of secretions that have been choking the large and small bronchi may cause an immediate striking change in the physical findings. Dullness, distant breath sounds with few or no post-tussic râles, which are the usual findings when the bronchi are choked with secretions, become, respectively, resonance or slight dullness, clear breath sounds with many crepitant râles and rhonchi after the previously choked bronchopulmonary areas have become aërated.

Roentgenology

Mention has already been made of those occasional cases of bronchiectasis without pneumonitis in which no abnormality can be seen in the roentgenograms. In other cases peribronchial thickening is revealed as increased bronchial markings or as ring shadows. More extensive infiltration around the bronchial walls or in the parenchyma may appear as a patchy infiltration resembling bronchial pneumonia, tuberculosis, fungus disease or the congested pulmonary vessels of congestive cardiac failure. Faint lines

of fibrous tissue may be only indistinctly seen but their contraction may be manifested by retraction of the mediastinum and diaphragm and by a visible, displaced interlobar fissure. Extensive cellular infiltration and parenchymal fibrosis appear as areas of heavy infiltration, perhaps interspersed with areas of emphysema, or they may occupy an entire lobe, which is usually much reduced in size. When such a contracted infiltrated lobe is the left lower, its shadow may lie entirely behind the heart and be invisible in a postero-anterior roentgenogram of standard density; the shadow can be readily seen in a lateral projection roentgenogram which is not overexposed, or in an overexposed or Potter-Bucky technic postero-anterior film. The diversity of the roentgenologic shadows seen in bronchiectasis is responsible for their rather frequent misinterpretation, and for the mistaken diagnoses of tuberculosis, fungus disease, congestive cardiac failure, pneumonia, pulmonary abscess, bronchogenic carcinoma, atelectasis, localized pleural effusion or empyema and other conditions. Andrus' article ably describes the roentgenographic findings in bronchiectasis.

Bronchograms

Iodized oil bronchograms are necessary to establish a definite diagnosis. Although the introduction of the oil into only the lower parts of the lungs, followed by the making of a postero-anterior roentgenogram, and without special preparation of the patient, may reveal the presence of bronchiectasis, this technic is so antiquated and furnishes so little information about the extent and position of the lesions, that it should be promptly discarded. A more or less routine procedure should be followed in connection with the making of bronchograms:

1. A lateral projection roentgenogram and stereoscopic, postero-anterior, standard-technic roentgenograms should be obtained before the bronchograms are made in order to learn as much as possible about whatever abnormal shadows may be present in the lungs, since prolonged retention of iodized oil in the lungs may for months or even years prevent an accurate interpretation of pulmonary shadows.

2. Virtually every patient having bronchiectasis, or suspected of having it, should have a bronchoscopic examination. Bronchoscopy alone gives accurate information about such obstructing bronchial lesions as carcinoma, foreign body, and pyogenic granulation tissue. The chemical shrinkage of swollen bronchial mucosa and the thorough aspiration of all secretions that can be reached with a bronchoscopic aspirator not only benefit the patient but also clear the bronchi for the reception of the iodized oil that should be introduced within the following 48 hours, postural drainages being used in the interval in order to keep the bronchi as clear as possible.

3. Iodized oil should not be introduced into the lung within three weeks following the disappearance of an attack of acute pneumonitis or any febrile episode which presumably had its origin in the pulmonary lesions. The

breaking of this rule may result in a serious, and occasionally fatal attack of acute pneumonitis.

4. Immediately after a postural drainage and after producing the same local anesthesia of the pharynx, larynx, trachea and bronchi which is used for bronchoscopy, the lipiodol should be introduced in such a way that the bronchi of all five lobes of the lungs are well coated. This may be done in two sittings, but preferably in one sitting. A series of roentgenograms must immediately be made in certain specified projections that will permit an exact differentiation not only of the bronchi of the different lobes but also of the segments of the lobes, as these findings are essential for consideration of the advisability or inadvisability of lobectomy. A technic for the introduction of the iodized oil and for the making of the roentgenograms has been described in detail by Adams and Davenport. If, for any reason, any lobar, or segment of a lobar, bronchus has not been adequately filled for an accurate interpretation of the roentgenograms, another attempt to outline the defectively filled bronchus should be made a few days later, if a lobectomy operation is being considered. Although the demonstration of bronchiectases is the primary purpose of bronchograms, the persistence of a filling defect in any bronchus proximal to the bronchi of the fourth order in two or more series of bronchograms is of the greatest clinical significance since such a filling defect indicates not only that there is a probably harmful bronchial obstruction but also that bronchiectases presumably exist in the pulmonary segment beyond the obstruction. What has just been said does not refer to the filling defects which are almost constantly present in the small bronchi distal to those bronchiectases which have been outlined by the iodized oil, because these small bronchi are not constricted but are clogged with secretions and so have no room for the oil.

When treatment, particularly lobectomy, is being discussed while bronchograms are being studied, a statement is occasionally made to the effect that the bronchiectases are too few or too poorly developed to require active treatment. I have seen many patients with such lesions who had exceptionally severe and disabling symptoms (probably because of poor bronchial drainage) and other patients with extensive, well developed bronchiectases whose symptoms were relatively mild (probably because of good bronchial drainage). I have recently seen a woman having a few slightly widened bronchi in the middle lobe; a careful study of the bronchograms, however, revealed several areas of filling defect. A well known physician had assured the patient that she had no bronchiectasis and that a winter in a sunny dry climate would cure her. When I saw her at the end of the winter there were dullness and râles over a small middle lobe and the patient was excessively fatigued, greatly underweight, had a slight afternoon elevation of temperature, moderate cough and scanty sputum. Active treatment is urgently needed by this patient in spite of the apparent innocence of the few bronchiectatic lesions shown by the bronchograms.

Prognosis

Great variability in the clinical behavior of different cases of bronchiectasis has created considerable confusion about the prognosis. Some patients, particularly those whose illness has never required treatment in a hospital, enjoy moderately good health for a great many years. Other patients, usually those who have had repeated attacks of acute pneumonitis, are seriously disabled most of the time and are likely to die within a few years after the onset of the disease. There are, of course, many gradations of illness between these extremes. The conclusion of those clinicians who have made special studies of the prognosis is that it is much worse than those who have not investigated the matter believe. In this connection the reader is referred to the articles of Perry and King; Bradshaw, Putney and Clerf; Riggins; Findlay and Graham; and Roles and Todd. A mere list of the complications (only the last few being infrequently seen) indicates the potential gravity of bronchiectasis: repeated attacks of acute suppurative pneumonitis; pulmonary abscess or gangrene; septicemia; pleural empyema; spontaneous pneumothorax; brain abscess or meningitis; repeated severe hemoptyses; pulmonary fibrosis, emphysema, cor pulmonale, myocardial degeneration, cardiac decompensation; nephritis and amyloid disease; suppurative pericarditis; suicide; arthritis, and carcinoma from metaplasia of chronically inflamed bronchial mucosa.

Treatment

Elastic bronchial walls apparently may be stretched or dilated as a result of atelectasis and later resume their normal caliber with the disappearance of the atelectasis, provided infection of the bronchial walls has not occurred, destroying their elasticity. This train of events, which is probably rare, is generally believed to represent the only instance in which bronchiectases disappear, with or without the aid of treatment. Only a few cases have been reported in which bronchiectases that were infected and had produced the clinical picture of bronchiectasis, later disappeared.

The aim of treatment, therefore, is either to reduce, as far as possible, the ill effects of the permanent lesions by nonsurgical means, or to remove completely the lesions by the operation of lobectomy. Since nonsurgical treatment is necessarily only palliative, and since even a patient whose condition has been greatly improved by it, is constantly in danger of suffering a relapse, lobectomy is obviously the only form of treatment that can produce a cure.

Lobectomy is, without question, overwhelmingly the treatment of choice for those patients (1) whose age, cardiorespiratory functional reserve and general condition are suitable; (2) whose lesions are restricted to one lobe, or to the right lower and middle lobes, or to the left lower and lingular ("left middle") lobes or, in some cases, to all the lobes of one lung (total pneumonectomy) or to one lobe of each lung or to two lobes of one lung and one

lobe of the other lung (bilateral lobectomy); (3) who have failed to attain a satisfactorily stable condition of improvement from nonsurgical treatment. In view of the potential gravity of bronchiectasis, because of the ever present danger of some serious complication, the validity of the third condition, just mentioned, is subject to question, especially in young patients with lesions in only the lower lobe, or lower and middle lobes, of one lung. The risk of lobectomy in children as young as five years of age is apparently less than average, and in adults in the fourth and even fifth decades of life not much greater than average. Special additional reasons for performing lobectomy in childhood are that the dangers of bronchiectasis are particularly great then and that the removal of the lesions makes probable a normally long life of health, in place of a probable short life of varying degrees of illness and disability.

The factors that determine a particular patient's suitability or unsuitability for lobectomy are so many and complex in their inter-relationships that unqualified indications for the operation cannot be given. Obviously the indications are far broader at present, when the surgical mortality * is approximately only 5 per cent in certain clinics, than in 1932 when Lilienthal reported a surgical mortality rate of 62.5 per cent for his 40 cases of partial or complete lobectomy. The present mortality rate varies rather widely from clinic to clinic. Dolley and Jones in 1939 collected 549 cases of lobectomy for bronchiectasis in which there had been 127 (23 per cent) deaths, but these 549 cases include early series of cases. The death rate in the cases collected after 1929 was about 18 per cent. In 1939 Bradshaw, Chodoff and Deardorff reported three deaths in 30 cases, or 9.6 per cent (sic). Edwards in 1939 reported 20 (12.5 per cent) hospital deaths in 166 lobectomy operations on 160 patients, and six later deaths, but in his last 54 cases there were only two deaths (3.7 per cent). Perry and King in 1940 reported that Churchill had had only four deaths (3.3 per cent) in 122 lobectomy operations on 116 patients. Alexander and O'Rourke report three deaths (4.3 per cent) directly connected with operation, and two late deaths (2.9 per cent) in 70 consecutive patients operated upon by Alexander or Haight. One of the late deaths occurred six months after operation from a fulminating pneumonia in a patient who developed a pulmonary abscess three months after operation; the other late death occurred five months after operation from a bacteremia which arose three days after the changing of an empyema drainage tube three months after operation in a patient who was doing well except for a persisting small empyema pocket.

The indications for lobectomy may become further extended in certain cases of multiple-lobe bronchiectasis by the wider application of Churchill and Belsey's suggestion that in certain cases only affected segments of lobes be removed. This principle has been applied for a number of years in the

* These figures express, with a few exceptions, the rate for the removal of the lower lobe, or lower and middle lobes, of one lung. The rate for bilateral lobectomy is considerably higher.

removal of the lingular segment of the left upper lobe, which is technically simpler and safer than for any other lobar segment.

Being a surgeon who has performed lobectomy operations in increasing numbers during the last 15 years and having seen many patients transformed from a state of prolonged wretched ill health to perfect health, I am as aware as anyone could be of the value of lobectomy. But I also know that there are a great many bronchiectasis patients whose cases are not, for various good reasons, suitable for lobectomy, and I know from long experience that a majority of these patients, although unfortunately not all, can be greatly helped by the faithful use of nonsurgical measures. These measures cannot cure the disease and only rarely do they bring about even a temporary complete disappearance of symptoms, but they frequently so greatly improve the symptoms that they become minor annoyances rather than the cause of distressing disability. I am, therefore, unable to understand the pessimism of Riggins and of Lisa and Rosenblatt about nonsurgical treatment for the relief of those patients for whom the curative operation of lobectomy cannot be performed. Lisa and Rosenblatt state in their 1943 book on bronchiectasis that "some palliative procedures have been retained chiefly as adjunct procedures to lobectomy," and in the summary of the book not one word is said about nonsurgical treatment. Many readers will infer that the authors of this book believe that lobectomy is suitable for practically all bronchiectasis patients. Unfortunately many are not suitable and these should receive medical treatment.

Postural drainage is the most valuable of the nonsurgical therapeutic measures and, yet, it is usually used inefficiently. Its aim is to improve bronchial drainage, thereby lessening toxic absorption from retained bronchopulmonary secretions and reducing infection in the bronchi and lung. The maximal good effect would be obtained if all free secretions could be drained away as rapidly as they form; some clinicians have attempted to do this by keeping their patients continuously in bed for several weeks or months, the foot of the bed being elevated about 15 inches. Almost as effective, and more practical for patients who need not remain in bed, is the use of postural drainage every two hours * from the time of awakening until bed time (and at night, if the patient should awaken), the schedule being so adjusted that no postural drainage comes within an hour after a meal. Postural drainage should be carried out by the patient's leaning over the edge of a bed or table sufficiently high to cause his torso to be inverted perpendicularly when his hands are resting on the floor. The taking of half a dozen deep breaths before each half dozen hard coughs loosens the secretions better for expectoration and aërates the affected portion of the lung better than if the inversion and coughing are alone relied upon. Cycles of deep breathing and hard coughing should be repeated until the patient feels that no more secre-

* After two or three weeks, if the secretions have been greatly reduced, the interval between drainages may properly be lengthened to three or even four hours.

tions can be loosened for expectoration. The duration of a postural drainage should not be prescribed in minutes.

Patients who are not accustomed to an inverted posture may at first become dizzy and need to be helped up before the drainage has been completed. Patients who have full-time jobs may be unable to find a high table in a non-public place where postural drainage can be carried out during working hours. Bending as far forward as possible at the hips in a lavatory (the knees being bent, the hips high and the head close to the floor) serves as a reasonably satisfactory substitute for the regular position. Although the inverted position that has been described is the one that produces the best drainage in most patients, some learn from trial that other postures are more effective in their particular cases, such as lying upon the back, the face or one or the other side, with or without the foot of the bed elevated. These modified postures are suitable for patients who are too ill or feeble for the rather strenuous inverted posture. Occasionally, patients find that expectoration is freest in the sitting or standing position, but that the preliminary inverted posture loosens the secretions for ready expectoration. A bronchoscopy carried out immediately after a postural drainage determines the relative number of retained secretions and, therefore, gives an indication of the probable effectiveness of postural drainage.

Every bronchiectatic patient should have at least one bronchoscopic examination, not only because some otherwise undetectable, important intrabronchial lesion may be discovered but also because the aspiration of secretions and the chemical shrinkage of the bronchial mucosa often bring about improvement in the symptoms, which in occasional cases (notably in children, and also in adults) is astonishingly great. Bronchoscopy is also of great value in preventing the development of bronchiectasis in *early* cases of pneumonitis or "unresolved pneumonia." The ordinary bronchoscopic treatment, in which a few of the secretions are aspirated and in which the mucosa is treated for only a few moments, is of little value. An effective treatment, which should be immediately preceded by a postural drainage and which may occupy from 15 to 30 minutes, requires (1) that the bronchi containing secretions should be repeatedly aspirated until all free secretions have been removed, both before and after the mucosa has been shrunken and the patient has repeatedly coughed on command, and (2) that equal parts of 2 per cent pantocaine and 1 to 1,000 epinephrine solutions, or other shrinking drugs, be directly applied, step by step, to all parts of the mucosa that are swollen, and that an excess of the solution in the gauze pledgets be squeezed into those bronchi of the affected parts of the lung that are too small to be directly reached by the pledgets, or that a small amount of the solution be injected into these bronchi.

The effect of this treatment is to empty and open the choked bronchi, most of which (including the bronchiectases themselves) are distal to the field of bronchoscopic vision. The small bronchi in the peripheral portion of the

bronchiectatic lobes cannot be reached by the bronchoscopic aspirator but they can be at least partially emptied of secretions by voluntary coughing after all secretions proximal to them have been aspirated. Air enters more and more deeply into the lung as the secretions are aspirated and coughed from the bronchopulmonary areas that had been drowned in secretions. The aëration of the peripheral portions of the affected lobes is the most important objective of bronchoscopic treatment. Aëration of the small bronchi and alveoli is the most effective means of aiding the patient to evacuate additional secretions by coughing, both during and following bronchoscopy. Deep breathing and coughing at from 15 to 60 minute intervals during waking hours for one or two days after a bronchoscopic treatment, and the faithful carrying out of postural drainages indefinitely after bronchoscopy are obviously important in maintaining aëration and maximal evacuation of secretions. Evidence that a choked portion of a lung has been drained and aërated is often furnished by the change from dullness to resonance, from distant or almost absent breath sounds to distinct breath sounds, and from few or no râles to many râles, as a result of a particularly effective bronchoscopic treatment, and sometimes as a result of only a postural drainage. The length of time during which aëration and drainage are maintained probably depends in part upon the faithfulness of the patient in carrying out the prescribed postural drainages, and in part upon whether the good effects of aëration and of whatever reduction in infection of the bronchial mucosa occurs as a result of the improved drainage predominate over a recurrence of the mucosal swelling, which presumably may occur as a secondary reaction to the drugs that were used to shrink the mucosa.

Experience has shown that in a few cases, one bronchoscopic treatment removes all the particularly distressing symptoms for an indefinite period of time. In a greater number of cases, no relief of symptoms occurs and in a very few cases the symptoms are made worse through an acute attack of pneumonitis. In a majority of patients a satisfactory improvement takes place but, in the course of a week, or several weeks or months, a relapse occurs, calling for another bronchoscopic treatment. In those patients who are indefinitely relieved by one bronchoscopic treatment, or who are not relieved at all, further treatments are obviously not indicated. In the other patients, repeated bronchoscopies are indicated at whatever intervals (five days, several weeks or months) the circumstances require. I have had no experience with bronchoscopic irrigations; from what I hear, I believe that they are, at best, no more effective than the treatment that has been described in this article and that they expose the patient to the danger of an attack of pneumonitis.

Since the primary purpose of nonsurgical treatment is to bring about the maximal evacuation of secretions, cough medicines that check the cough reflex are not only not helpful but are harmful, and measures that promote expectoration are beneficial. Such expectorants as ammonium chloride, iodides, ipecac, steam inhalations that may be medicated with benzoin or

menthol, and the inhalation of a nebulized spray of 1 to 100 dilution of epinephrine solution may prove useful if the secretions are thick and especially viscid, and if expectoration is difficult. Some clinicians recommend the therapeutic instillation of iodized oil into the affected bronchi every week or so; they say the mucosa is thereby soothed, cough, stagnation and fetor of the secretions relieved and the general condition of the patient improved. I have seen such improvement too infrequently after the diagnostic instillation of iodized oil to justify its therapeutic use in my clinic, and I believe there is a definite risk of the lung's being harmed by the locking in the alveoli of parts of repeated injections of the oil.

Only in exceptional cases has chemotherapy proved useful. Intravenous arsenicals, which are especially dangerous in patients having a prolonged suppurative disease, have occasionally reduced pulmonary infection when it is caused chiefly by the Vincent's group of organisms. The sulfonamides, whether given by mouth or by nebulizer, have been disappointing in chronic bronchiectasis although, in a few patients, an excellent effect has been produced.

Treatment of infection in the nasal sinuses, nose, mouth and pharynx should be used and may improve the bronchiectasis symptoms. I do not recall a single case, however, in which so-called radical sinus surgery, carried out in the presence of troublesome bronchiectasis, has either completely cured the sinus disease or importantly improved the bronchiectasis symptoms. In my experience radical sinus surgery is much more likely to be effective if deferred until several months have passed after the bronchiectasis has been cured by lobectomy or improved by other treatment. In a few cases, the sinus symptoms will have improved so much that radical surgery is not required.

General hygienic measures are indicated in most cases of bronchiectasis. Ideally, patients who have even mild fever and who are fatigued and underweight should be put to bed for a period of weeks or months under the sanatorium type of regimen or should at least spend long hours in bed at night and two hours in bed after lunch. I am familiar with the work of a pediatrician who has brought about almost miraculous improvement in several children I have seen merely by enforcing regular habits of life, regular postural drainages and, particularly, by expert feeding. Generalized heliotherapy may be helpful as a hygienic measure, but should not be used in febrile patients or in those subject to recurrent attacks of pneumonitis. Anemia should, of course, be treated, by blood transfusions if necessary. Patients who live where the winters are cold and stormy may be benefited by spending the winters in a sunny dry climate which, in some patients, prevents the occurrence of repeated colds and which may also reduce the severity of the nasal sinus symptoms, and the amount of cough and sputum from the bronchiectasis.

Although Watson and Kibler believe that allergic desensitization is highly effective in the treatment of bronchiectasis, I share the experience

of many clinicians in finding it disappointing. The only cases in which I have seen good results from any form of desensitization (including the use of autogenous or mixed stock vaccines for bacterial desensitization) are a few having characteristic symptoms of bronchiectasis but not having any bronchiectases, the symptoms being due to a true allergic bronchitis. In such cases, bronchograms show that the bronchi are abnormally narrow and bronchoscopy reveals swollen pale mucous membrane and mucopurulent secretions.

In certain cases of bronchiectasis with repeated severe hemoptysis, temporary phrenic paralysis may stop the bleeding, but this operation should not be used if the patient has difficulty in raising his bronchopulmonary secretions. In rare instances, retention of secretions in a large bronchiectatic abscess, or in a parenchymal abscess associated with bronchiectasis, may call for surgical drainage of the abscess.

I shall not discuss in this article those forms of therapy that I believe should not be used, namely, induced pneumothorax, roentgen-ray therapy, "the thirst cure," and those many operations that have been proposed, or used with poor results, before the operation of lobectomy was developed to its present status of safety and effectiveness.

Summary

The many causes of confusion concerning the nature of bronchiectasis, the variability of its clinical behavior, the diagnosis and treatment are discussed. The most frequent sources of error in the management of the disease are considered in detail.

The present safety of pulmonary lobectomy has solved the problem of treatment for approximately half the bronchiectasis patients, but the other half are, for various reasons (especially because of extensive bilateral lesions) not suitable for the operation. Nonsurgical methods of treatment, if properly and faithfully carried out, can be made effective in greatly alleviating the distressing symptoms of the disease in a large majority of patients, in spite of the pessimistic opinions about the value of nonsurgical treatment that have recently been expressed by a number of physicians.

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STERNAL PUNCTURE AS A PRACTICAL DIAGNOSTIC PROCEDURE *

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Since the introduction of the procedure by Arinkin [1] in 1927, sternal puncture has been very widely used. Notable contributions to the scientific knowledge of the cytology of bone marrow obtained in this way from patients with various diseases have been made by Arinkin,[2] Nordenson,[3] Segerdahl,[4] Young and Osgood,[5] Vogel, Erf and Rosenthal,[6] Jones,[7] Scott,[8] and others. Most of the punctures reported in the literature have been made for the scientific study of diseases of the hematopoietic system. There are many reports of cases in which the diagnosis was arrived at solely by means of the sternal puncture, but no mention is made of how frequently one may expect to diagnose a given case in this way. Indications for the use of sternal puncture as a diagnostic method have not been clearly established, and the interpretation of marrow findings has not been sufficiently simplified to be of practical value to the average physician.

Recently attempts at evaluation of the procedure have been made by three groups of workers. Kandel and Leroy [9] found sternal puncture to be of relatively little value in the diagnosis of their cases and are of the opinion that "thorough clinical investigation deprives the biopsy of sternal marrow of many of its uses." Falconer and Leonard [10] say: "It is interesting to note that the diagnosis arrived at after thorough study of each case before sternal marrow aspiration was rarely changed by the data subsequently obtained through the study of the marrow cells." No one will argue against the advisability of carrying out a thorough clinical investigation before doing a sternal puncture, unless possibly time is an important factor. However, in many cases exhaustive study ends in no diagnosis or in a questionable opinion and it involves time, expense, and an extended period of worry for the patient and his family. Mendell, Meranze and Meranze,[11] however, say that sternal marrow aspiration "is indicated in all cases suggesting disorders of the blood-forming organs or reticulo-endothelial system." This seems to us to be overly enthusiastic as most cases can be diagnosed without recourse to sternal puncture.

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At the present time, therefore, it is desirable to know whether sternal puncture is an additional diagnostic procedure of reliability, when it should be undertaken, and what practical benefits may be expected from it. The purpose of this paper is (1) to give in detail certain points of practical value in technic and interpretation, (2) to suggest a simple method of reporting the marrow findings so that an understanding of the state of the marrow can be more easily obtained by the average physician, (3) to present the clinical value of sternal puncture under actual working conditions, and (4) to establish indications for its use.

Technic

All authors have agreed that sternal puncture is a very simple matter. A successful puncture, however, requires a number of rapidly executed technical procedures, and the failure of any one of them may result in an unsatisfactory sample. Unless a novice at the method is forewarned, it is almost certain that his first attempts will yield unsatisfactory results. Some authors advocate very complicated methods of handling the sample of marrow after it is withdrawn. These seem to us quite unnecessary for practical purposes. We have given our technic in detail in the hope that time and effort will be saved for beginners, and that assistance will be given those who have already been disappointed in their efforts to use this procedure.

The technic used in our punctures is very similar to that originally described by Arinkin.[2] The needles are 18-gauge spinal puncture type with a heavy finger grip and a stylet (figure 1). They are cut so that the needle portions are 2, 1.5, and 1 cm. in length. The two longer needles are used for adults, the choice depending upon the build of the individual, and the smallest one is used for infants and children. The shortness of the needles precludes the possibility of accidental perforation into the anterior mediastinum and prevents bending of the shaft of the needle during its insertion. The puncture is made in the midline of the body of the sternum at the level of the third costosternal articulation. This site is easily found, even in obese patients, by using the sternal angle, which marks the second rib, as a reference point. Whenever possible, the lateral margins of the sternum are grasped between the first and second digits of the hand not performing the puncture so that the midline of the sternum may be selected accurately. Proceeding too far laterally may result in failure to enter the marrow cavity. Other levels * may be used at the discretion of the operator if this site is not available or if a check is desired. In children it is advisable to do the puncture in the third interspace because in some individuals the first and second sternebrae do not unite until adult life is reached. Strict surgical asepsis must be maintained. The skin, subcutaneous tissue and periosteum are infiltrated with novocaine. Some pain is commonly caused when the hypodermic needle penetrates the periosteum to produce local anesthesia. The

* In six cases in our series similar marrow pictures were found when multiple punctures were done at various levels in the same patient.

periosteum causes a firmer feeling of resistance to the needle than the subcutaneous tissue, and an appreciable sensation of thickness. Upon piercing it, the needle tip strikes the bony anterior plate of the sternum. The final injection of novocaine is then made. A very small amount is sufficient. A total of three cubic centimeters will usually accomplish all necessary anesthesia of the skin and underlying structures. When properly carried out, sternal puncture is not a very painful procedure. Frequently it appears to

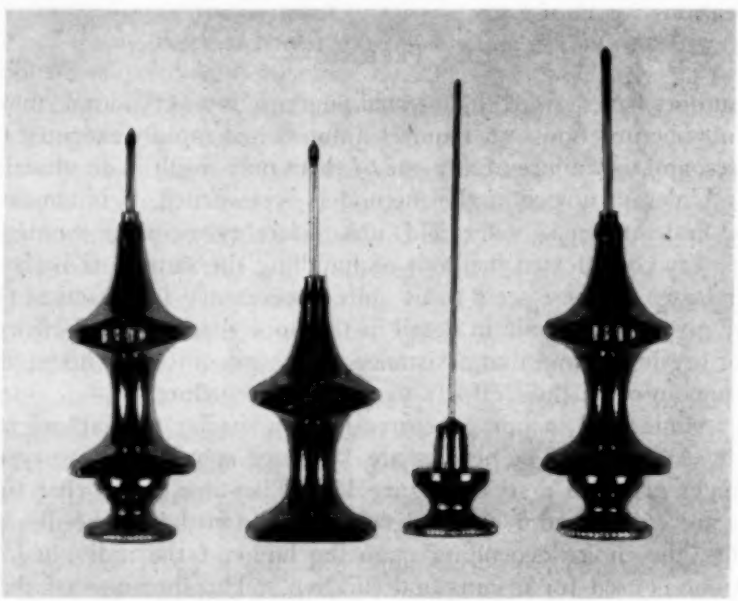

FIG. 1. Full sized photograph of the needles used in doing sternal punctures. The stylet has been removed from the center needle.

produce no appreciable discomfort. The puncture needle is inserted vertically, and the outer table of the sternum is pierced by a rotary movement of the needle under firm pressure. The stylet must be held down firmly so that no bone spicules can enter the tip of the needle to block it during penetration of the outer table. Boring is continued until the needle is firmly fixed in the bone. No dependence is placed on sound or feel when the bone is pierced, as in many punctures there is no indication that the medullary cavity has been reached, i.e., the so-called "give" may be absent. When the needle is firmly fixed in the sternum, the stylet is removed, a tuberculin syringe is attached to the needle, and aspiration is attempted. If no marrow fluid appears, the stylet is replaced, the needle is advanced a little farther, and aspiration is again tried. This is continued until marrow fluid, which has the gross appearance of ordinary blood, appears in the syringe. This may be preceded and accompanied by a painful sensation in the chest, evidently the result of producing a negative pressure in the marrow cavity. The pain is never

severe in character. Occasionally, no material is obtained with the tuberculin syringe, and it is necessary to use a larger syringe (5 to 10 c.c.) to produce a greater suction, in order to be sure that no cells can be detached from inside the marrow cavity. This is more likely to occur in cases in which there is a replacement of bone marrow by pathological tissue as in Hodgkin's disease, reticulosis, and other similar diseases.

One-tenth to 0.2 c.c. of marrow fluid is withdrawn. This quantity has given the best results in our punctures. Aspiration of more fluid serves no purpose and in some instances greatly dilutes the marrow sample with peripheral blood. Taking a smaller amount sometimes results in failure to aspirate a sufficient amount of marrow for study. There is always an admixture of sinusoidal blood in the sample, the amount probably varying from puncture to puncture, as well as with the volume of fluid removed. Therefore, total counts of cells in the puncture fluid have not been done in our study.

Care must be taken to stop suction before the needle and its attached syringe are withdrawn, together, from the sternum. It is essential that the marrow sample remain in the puncture needle and the lower part of the syringe. It is necessary therefore, to hold the plunger firmly in place, during withdrawal or the marrow fluid may be sucked up into the syringe when the needle comes out of the bone, or the weight of the plunger may force the fluid out of the needle before the operator is ready for it. As soon as the needle is withdrawn from the sternum (with the tuberculin syringe attached) it must be quickly turned to a horizontal position to prevent the extrusion of drops of marrow fluid at the free end. A sterile compress is then applied to the puncture wound and held in place by adhesive for 48 hours.

The most satisfactory portion of the specimen for study is that which enters the needle last and, therefore, is used in making the first smears. The portion which enters the needle first, in our experience, may contain only sinusoidal blood. It is necessary to work rapidly in making the smears as clotting occurs quickly in the needle. Coating the needle and syringe with sterile vaseline allows a more leisurely procedure, but it has not been found to be really necessary. Anticoagulants such as sodium citrate or potassium oxalate sometimes interfere with the staining of the marrow cells.

To make the smears, the tuberculin syringe and its attached puncture needle are held horizontally, with the opening of the needle facing downwards, and small drops of marrow fluid are made to appear at the opening by gently pushing in the plunger. Great care must be used in doing this or the drops expressed from the needle will become too large. A number of dried smears, at least 12, are made directly on scrupulously clean covers slips only. The drops of marrow fluid placed on the slips for smearing must be very small. The cells on the smears should lie close together but not overlap. If the films are too thick they do not stain well. If they are too thin, many of the more fragile cells will break up. The smear must be dried quickly

or it will not stain properly. All smears of marrow in which fat cells are present in the marrow cavity contain fat droplets. This fact may be used as an indication that the aspirated material actually came from the marrow cavity, a point which is sometimes doubtful in extremely hypoplastic marrows. The smears are stained with Wright's stain, which we have found to be quite satisfactory. The stain is carefully made up and is used without dilution. Wright's stain is easier to use than May-Gruenwald-Giemsa, and moreover all physicians are familiar with the appearance of cells stained by this method. The importance of good smears and proper staining cannot be overemphasized.

To make reticulocyte counts, scrupulously clean slides are prepared by flooding them with a saturated solution of brilliant cresyl blue in 95 per cent alcohol, draining off the excess and allowing them to dry in a vertical position. If small particles of dye appear on the slide, the marrow film will not spread evenly. Such particles can be removed by gently polishing the dried cresyl blue on the slide with lens paper. A small drop of marrow fluid is placed on a cover slip which is then inverted upon the cresyl blue slide. The edges of the coverslip are rimmed with vaseline to prevent evaporation and subsequent crenation of the erythrocytes.* The count must be made within one hour after preparing the film if the slide is left at room temperature. For the sake of uniform procedure, the second drop which comes out of the needle is used to make the reticulocyte preparation. The nuclei of all the cells stain heavily and this slide is also used for estimating the degree of cellularity of the marrow. Naturally, the cellularity may be also estimated from the dried smears.

Supravital preparations are also made of every puncture for comparison with the dried films. These are not an essential part of the procedure, but may be of help in the identification of monocytes.†

Material

Our material consists of 140 cases of diseases of the blood and hematopoietic system and cases in which the possibility of such disorders entered into the differential diagnosis. Twenty punctures on patients ranging in age from 17 to 41 years without hematological disorders served as normal standards. Our differential counts on this latter material are in agreement with the results obtained by other authors for normal marrow.

* It is generally agreed that "wet" methods of counting reticulocytes are preferable to "dry" methods, as the latter do not always stain all the reticulocytes. The statement of Mendell, Meranze and Meranze that "reticulocytes in the bone marrow in relapse (of pernicious anemia) were too few to be counted" is not supported by this study. In our series the lowest reticulocyte count in the marrow in this condition was 0.4 per cent, and the most severely anemic case we have seen had 3.1 per cent.

† Vogel, Erf and Rosenthal found monocytes present in only two of 246 punctures. Monocytes can be identified in almost all punctures when studied with the supravital method, though it must be admitted that we have not been able to find them as frequently in the dried smears.

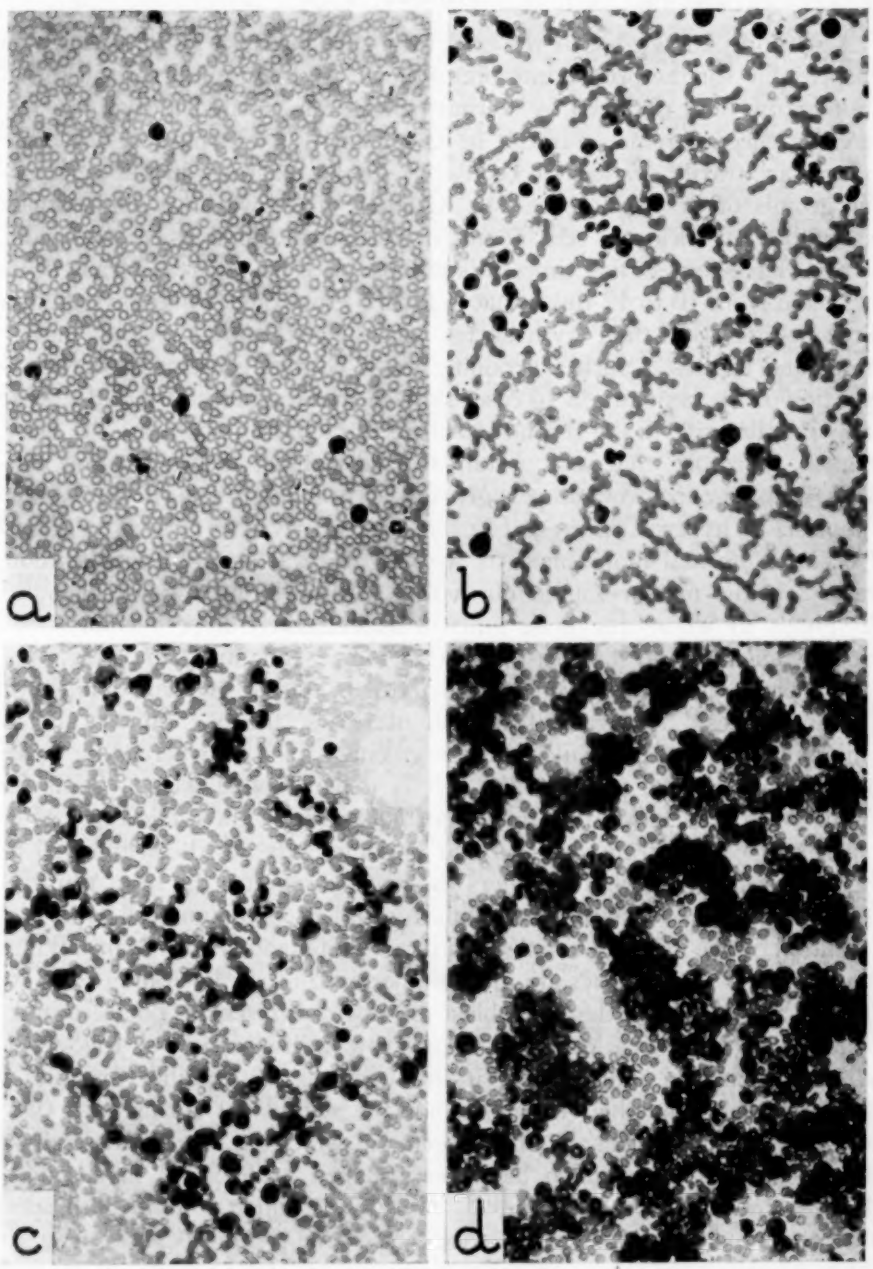

FIG. 2. Grades of cellularity found in smears of marrow aspirated from sternal punctures. *a*, Grade 1, from a normal individual; *b*, Grade 2, from a normal individual; *c*, Grade 3, from a normal individual; *d*, Grade 4, from a case of chronic myelogenous leukemia. The photographs show the dispersion of nucleated cells when viewed with the 16 mm. lens. × 170.

Cytology

A working knowledge of the cells in normal marrow is, needless to say, indispensable for the proper interpretation of the marrow picture in disease. The marrow fluid obtained by sternal puncture in normal individuals is, in our experience, extremely variable in its cellularity. For purposes of record, we have arbitrarily graded the cellularity of the marrows in our series into four groups or grades (figure 2). Grade 1 marrows have approximately the number of nucleated cells found in peripheral blood smears. Grade 2 marrows have four to five times this number of cells, whereas Grade 3 marrows have from 10 to 12 times that number. In Grade 4 marrows there are more nucleated cells than erythrocytes, and the cells appear on the smears in clumps and masses. Such a grouping is, of course, grossly inaccurate, but repetition of the puncture in 16 cases showed that the individual had the same grade of cellularity in the second puncture as he had in the first. It may be assumed, therefore, that with a standardized technic, such a grading of the cellularity of the marrow samples gives at least a rough idea of the degree of hypoplasia or hyperplasia present in the marrow cavity. Grades 1, 2, and 3 all occur in normal individuals, as well as in a variety of diseases, though Grade 2 is the most common normally. Grade 4 marrows occur only in individuals in whom the bone marrow is extremely hyperplastic, such as chronic leukemias and some cases of pernicious anemia and hemolytic anemia.

The predominant cells in normal marrow belong to the neutrophilic series of granulocytes. In Grade 1 normal marrows, the one numerically predominant cell is a neutrophile with a segmented nucleus, whereas in Grade 3 normal marrows the predominant cell is a neutrophile with a band form (single lobed) nucleus. In Grade 2 normal marrows these two types of cells occur in almost equal numbers so that in some marrows the segmented neutrophiles predominate and in others the band forms are the most numerous. How much of the variation in cellularity and predominant cell type is due to dilution of the marrow sample with peripheral blood is at present unknown. The older cells of the series are more numerous, but all the younger cell types down to and including the myeloblast are always present. The terminology applied to the granulocytic cells of the marrow in this paper is as follows: (1) Cells which contain only specific (in this instance neutrophilic) granules and are distinguished by their nuclei include the segmented forms with two or more lobes in the nucleus; the band forms in which the nucleus has only one lobe; metamyelocytes, which have bean shaped nuclei; and myelocytes, in which the nucleus is round or oval. (2) Cells which contain both specific (neutrophilic) and azure granules are termed the promyelocytes. (3) Cells which contain only azure granules or are completely agranular are called leukoblasts and myeloblasts. Leukoblasts contain azure granules, may or may not have nucleoli, and have a definite nuclear membrane. Myeloblasts contain nucleoli, may or may not have azure granules in the cytoplasm, and the nuclear membrane is indistinct. Not all investigators recognize a leuko-

blast stage; such cells are probably classified by them partly as promyelocytes and partly as myeloblasts. Though of great theoretical interest, this question has at the present time no practical importance in diagnosis. In our material, the actual percentages of neutrophilic cell types based on differential counts of 500 cells from smears stained with Wright's stain on 20 normal marrows are as follows: * segmented neutrophiles 7.4–25.0 per cent, band forms 17.6–46.4 per cent, metamyelocytes 5.6–14.2 per cent, myelocytes 3.2–10.6 per cent, promyelocytes 2.2–8.0 per cent, leukoblasts, 0.4–3.0 per cent, myeloblasts 0.4–2.0 per cent.

Eosinophilic cells are also present in small numbers, 0.6 per cent–5.5 per cent. Most of these cells are the more mature forms, segmented and band forms, eosinophiles. Eosinophilic promyelocytes are rarely seen in normal marrow. Even smaller numbers of basophilic cells are normally found—from none at all to 0.8 per cent, almost all of them mature.

The cytology of the development of the red cells has been very thoroughly studied by Jones,[7] from whose article the substance of this section has been taken. In normal marrow, the erythroid cells are all of the normoblastic line. The earliest recognizable cell of this line is the pronormoblast, which is somewhat similar to the myeloblast in appearance. It is a large cell with a large nucleus, which may contain distinct nucleoli. It differs from the myeloblast in having a more condensed and homogeneous and more basophilic cytoplasm which contains no azure granules. The strands of chromatin in the nucleus are thicker than in the myeloblast, and there is not as much parachromatin. The next stage in the development of normal red cells is the basophilic normoblast, which has no nucleoli and does not in any way resemble the myeloblast. The cytoplasm is even more basophilic than in the pronormoblast, though it is sometimes not as homogeneous and condensed. As the pronormoblast matures, the individual granules of chromatin begin to fuse together or clump, and notches and crevices appear in the parachromatin, so that in the basophilic normoblast the chromatin has the appearance of coarse granular filaments. In late stages, some of these cells may show a wheel spoke (Radkern) arrangement of chromatin in the nucleus. The nucleus is smaller in proportion to the amount of cytoplasm than in the preceding stage. Hemoglobin is then developed in the cytoplasm, so that the intense basophilia is lost, making the polychromatic normoblast, and when the full complement of hemoglobin is present, the cell is called the orthochromatic normoblast. The nucleus becomes progressively more pycnotic during these changes and is finally dissolved, broken up or extruded from the cell, making the normal-sized erythrocyte. The actual percentages of erythroid cell types in our normal marrows are as follows: pronormoblasts 0.4–1.4 per cent, basophilic normoblasts 0.6–3.2 per cent, polychromatic normoblasts 2.6–17.6 per cent, orthochromatic normoblasts 0.4–4.8 per cent.

* All data on differential counts given in this section are 90 per cent central normal ranges, determined by Thompson's [12] method.

Marked hyperplasia of the normoblastic cell line, with an increase in the percentage of all its cell types, occurred in our series of cases in iron deficiency, acute hemolytic and sickle cell anemias, in the anemia due to acute hemorrhage, congenital hemolytic jaundice, and in secondary polycythemia. A lesser degree of hyperplasia was found in many other conditions.

A second type of erythroid cell which is never found in normal marrow is, however, present in some hematological disorders such as pernicious anemia in relapse, achrestic anemia and sprue, and occasionally in leukemia, hemolytic anemia, "aplastic" anemia and certain other diseases.[13] These cells give rise to the large-sized red cells (megalocytes) which are characteristic of the macrocytic hyperchromic anemias, and are known as the megaloblastic line of cells.

Many hematologists are apparently not aware of the existence of this second type of developing red cell * probably because they rarely occur in the peripheral blood and at the present time cannot be produced readily by experimental procedures. They are easily recognized in stained smears of the bone marrow in the above-mentioned diseases, but are less evident in supravital preparations.[14]

A complete series of developmental stages can be made out for them corresponding to similar stages in the normoblastic line. The earliest stage, the promegaloblast, is a large cell with a nucleus which is coarser than that of the myeloblast, and the cytoplasm is more basophilic. The cytoplasm is not, however, as dense and homogeneous as in the pronormoblast, and contains perinuclear light areas which give it a mottled appearance. The nucleus is smaller, compared to the size of the cell, than in the pronormoblast. The nucleoli are fainter in outline, and more or less masked by the chromatin reticulum. There is more parachromatin than in the pronormoblast, and less tendency for the chromatin to clump as the cells mature. The uniform distribution of chromatin throughout the nucleus and the absence of clumping of the chromatin threads until the very latest stage of development is reached is characteristic of this line of cells. The basophilic megaloblast is a smaller cell, but it is larger than the corresponding basophilic normoblast, and its cytoplasm is more basophilic and more homogeneous than that of the promegaloblast. There are no nucleoli. The chromatin reticulum is composed of small masses which are separated from one another by curved areas of parachromatin. In later stages, these curved areas become rounded, so that the

* There is at present considerable confusion in the terminology of the erythroid cells. The term megaloblast is used (1) as in this paper, to mean a dysplastic cell in which the nuclear chromatin forms a looser framework and has less tendency to form clumps and dense masses than does the nucleus of an erythroid cell of corresponding stage of development in normal marrow, and which is occasionally found in the peripheral blood but typically in the marrow in cases of pernicious anemia and sprue, (2) as the name of the earliest recognizable erythroid cell found in the marrow. The details of this controversy are beyond the scope of the present paper, but it is a matter of practical importance for if the second view were correct the marrow of pernicious anemia in relapse could not be distinguished from that of hemolytic anemia or from post-hemorrhagic marrow. For an exhaustive discussion of this problem, the reader is referred to Jones'[15] recent article.

nucleus looks rather like a sieve. The chromatin never forms a wheel type of nucleus. The sieve-like appearance of the nucleus persists through the polychromatic megaloblast stage, and only in the orthochromatic megaloblast, when the degeneration of the nucleus begins, is there any formation of large clumps and masses of chromatin. At a corresponding stage, the orthochromatic normoblast has a completely pycnotic nucleus. The cytoplasm of the megaloblastic cells remains disproportionately large compared to the size of the nucleus, and the disproportion grows more pronounced as the cell matures. Many large orthochromatic megaloblasts are found with small nuclei which are still vesicular and immature in appearance. Most megaloblastic cells are considerably larger than their homologues in the normoblastic line. However, after the nucleus has become completely pycnotic, it is sometimes difficult to distinguish small orthochromatic megaloblasts from large orthochromatic normoblasts. It should be borne in mind that all diseases in which megaloblasts are present also have normoblasts in the marrow to a varying extent.

In most of our normal subjects the reticulocyte count in the marrow was 0.5–2 per cent, but in one apparently normal individual, it was 3.7 per cent. We have, therefore, adopted 4 per cent as the upper limit of normal in order to be on the safe side, although this figure is probably somewhat too high.

Small numbers of lymphocytes, mostly of the small type, monocytes and plasma cells, all of mature form, are found in all normal smears. Immature forms of these cells are not normally encountered. At present, it is not known how many of the first two groups are actually in the marrow and how many are due to admixture of sinusoidal blood with the sample. Marrows from individuals having a lymphocytosis in the peripheral blood will naturally show an increased number of lymphocytes in the marrow smears. It must also be remembered that there are said to be occasional small lymph nodules in the marrow, and therefore an increase of lymphocytes is not necessarily of importance.

Megakaryocytes are easily recognized even with the low power objective. They are never numerous, and many of them are probably broken up in making the smears.

Cells in mitosis are found in all normal marrows, but they too are not numerous.

Reticulum cells and macrophages are occasionally found. "Ferrata" cells are in our opinion merely damaged cells, as has been suggested by Ringoen, but we doubt if they are produced solely from promyelocytes. They are absent from most smears, but sometimes occur in smears of abnormal marrows. We have not been able to find any small cells, either in the dry smears or in the supravital preparations which answer to the descriptions of "hematogones" as given in some of the literature. These cells are most probably overstained small lymphocytes.

The ratio of the number of all types of white blood cells and their pre-

cursors to the number of all types of nucleated red cells present in the sample we have called the myeloid-erythroid ratio. This ratio varies from 3:1 to 50:1 in normal individuals, and varies in the same individual on successive punctures. The variation is most probably due to the relatively small number of cells which are examined in a differential count as well as the error introduced by the unavoidable dilution of the marrow with sinusoidal peripheral blood. We have not found this ratio to be of much practical significance, although it is a convenient way of comparing the two groups of cells. Occasionally in anemias, this ratio approaches unity or is actually reversed, whereas in chronic leukemia the white cells greatly outnumber the erythroid series.

A certain number of cells in every puncture, from normal as well as abnormal marrow, cannot be identified, due to unavoidable injury to the cells in making the smears and to defects in the drying and staining process caused by fat droplets and the piling up of the nucleated cells. In normal marrow this number varies from 0.2 to 2.0 per cent, when the best parts of the smear are selected for study. Some abnormal marrows have many more cells which cannot be identified, the number depending partly on the skill, training, and optical equipment of the observer, but with a reasonably well-trained individual they are of no practical significance.

Clinical Material

A listing of all the diseases studied is given in table 1. After a careful review of these cases, they have been divided into three categories: (1) 74 cases in which sternal marrow punctures were actually indicated clinically; (2) 22 cases in which sternal punctures were done at the request of the attending physicians, but which by the criteria developed during this study were not indicated; (3) 44 cases in which punctures had been done to obtain specific information concerning the character of the marrow for research purposes, but which were not necessary for diagnosis.

The diseases included in the group of the 74 indicated cases are shown in table 2, and the value of these punctures is given in table 3. It can be seen that almost 65 per cent of the punctures for which there was an actual indication were of use clinically, and indeed the diagnosis was made by means of the puncture in 16.2 per cent of the cases where all other diagnostic means short of surgical biopsy had failed. In 35.1 per cent of the indicated punctures no results of clinical value were obtained, but nine of these 26 cases were of value for research purposes. Seventeen cases resulted in findings which were of no practical use either clinically or scientifically, and have been listed as being of "no value."

The results of the 22 punctures which were performed on request, though not actually indicated, are in marked contrast to the above findings: no information of clinical value was obtained from any of them. The correct diagnosis was made in one of these cases (4.5 per cent) by means of the

puncture, but this was of no practical help as it only established the correct type of an already diagnosed acute leukemia. Six of these punctures were of value for research work (27.3 per cent), but 15 of the 22 cases (68.2 per cent) were of no value at all. The pessimism shown in some of the more recent papers about the value of sternal punctures in diagnosis may be due to equally poor selection of cases for study.

TABLE I

Final Diagnosis on Cases Punctured

Agranulocytosis		5
Anemia		38
Achrestic	1	
Aplastic	2	
Hemolytic	4	
(Congenital jaundice—1)		
Hypochromic	12	
Macrocytic	2	
(Liver disease—1)		
Pernicious	16	
Sickle cell	1	
Banti's disease		1
Felty's syndrome		1
Hodgkin's disease		5
Infectious mononucleosis		2
Leukemia		31
Acute lymphatic	2	
Acute monocytic	1	
Acute myelogenous	7	
Chronic lymphatic	7	
Chronic myelogenous	7	
Aleukemic, myelogenous	7	
Leukemoid reaction		2
Lipoid histiocytosis		1
Malignant diseases		14
Mycosis fungoides		2
Myeloma, multiple		1
Osteosclerosis		1
Periarteritis nodosa		1
Polycythemia vera		2
Polycythemia, secondary		2
Sprue		1
Thrombocytopenia, primary		2
Thrombocytopenia, secondary		2
Wilson's disease		2
Miscellaneous		13
No diagnosis		11
Total		140

In the 44 cases which were done for research purposes, the correct type of an acute leukemia was established in one case (2.3 per cent); one case was diagnosed by means of the puncture, but could in our opinion have been diagnosed by other means (2.3 per cent); 34 cases were of research value (77.3 per cent); and eight punctures were of no value (18.1 per cent). No

TABLE II

Final Diagnosis on Clinically Indicated Punctures

Agranulocytosis		5
Anemia		10
Achrestic	1	
Aplastic	2	
Hemolytic	2	
Hypochromic	1	
Pernicious	4	
Banti's disease		1
Felty's syndrome		1
Hodgkin's disease		4
Infectious mononucleosis		2
Leukemia		13
Acute lymphatic	1	
Acute myelogenous	2	
Chronic lymphatic	2	
Chronic myelogenous	1	
Aleukemic myelogenous	7	
Leukemoid reaction		1
Lipoid histiocytosis		1
Malignant diseases		11
Mycosis fungoides		1
Myeloma, multiple		1
Osteosclerosis		1
Periarteritis nodosa		1
Thrombocytopenia, primary		2
Thrombocytopenia, secondary		1
Miscellaneous		8
No diagnosis		10
Total		74

TABLE III

Punctures Indicated Clinically

(74 cases)

Results of:	Number of Cases	Percentage of Group
Clinical Value	48	64.9
Correct diagnosis made by means of puncture	12	16.2
Correct diagnosis made by means of puncture but possible otherwise	2	2.7
Confirmatory in doubtful cases	4	5.4
Contributory to differential diagnosis	26	35.1
More rapid diagnosis	2	2.7
Prognostic value	2	2.7
No Clinical Value	26	35.1
Useful for research	9	12.2
No value	17	23.0

further reference will be made to the sternal punctures which were not clinically indicated.

No accidents or infections occurred in any of our punctures. There were no failures to obtain a sample except in cases in which it was subsequently proved that the bone marrow was completely aplastic, or in which it had been replaced by some other type of tissue.

The clinical value of sternal marrow punctures can best be shown by brief reference to the case histories.

Case Reports

I. Correct diagnosis made by means of puncture.

Case 1. A 78-year-old white man had been ill for two months with the chief complaints of weakness, swelling of the feet and extreme pallor. Slight splenic enlargement was found. The blood showed hemoglobin 6.6 grams, 45 per cent; red blood cells 2,224,000; color index 1.0; white blood cells 4,800; differential count: neutrophiles 68 per cent, small lymphocytes 28 per cent, eosinophiles 4 per cent.* Macrocytosis, anisocytosis, poikilocytosis and polychromatophilia were present in the red cells. No immature cells were found. Free hydrochloric acid was present in the gastric contents. On two occasions, a trace of blood was found in the feces by the benzidine test. A gastrointestinal series, intravenous pyelogram, barium enema and proctoscopic examination were negative. A later barium enema showed diverticulosis of the colon. He had been treated with very large dosage of parenteral liver extract and ferrous sulphate without improvement. At the time of puncture the latest blood count showed: hemoglobin 7.0 grams, 48 per cent; red blood cells 1,752,000; color index 1.4; white blood cells 4,000; neutrophiles 50 per cent, small lymphocytes 40 per cent, eosinophiles 10 per cent. A diagnosis could not be made. Sternal puncture revealed a hyperplastic marrow with a left shift in the granulocytic series (neutrophilic metamyelocytes predominating) and a marked hyperplasia of the red cell line. Large numbers of pronormoblasts and promegaloblasts were present as well as the later stages of both lines of cells. A diagnosis of achrestic anemia was made from the marrow findings in association with the clinical picture. Following puncture the patient was transfused and great improvement occurred. Gradual decline, necessitating more transfusions, followed.

This puncture enabled the clinician to obtain an insight into the case which otherwise would have remained extremely puzzling. There can be no question here of a case of pernicious anemia treated with an inadequate amount of liver extract, as this patient had received 15 units of liver extract daily for 15 days just before the puncture was performed, and moreover gastric free hydrochloric acid was present.

Case 2. A 34-year-old white, married female was admitted to the hospital with a temperature of 103° F. She had been ill with pain in the right hip and sacroiliac region for about five weeks, and had been treated in another hospital with a sulfonamide. She was referred because of persistent granulocytopenia. On admission, there was tenderness in the sacroiliac region bilaterally, in the right hip and later in both shoulder and acromio-clavicular joints. Pelvic examination showed bilaterally adherent and tender adnexa. A vaginal discharge was present in which no gonococci were found. No lymphadenopathy was present and the spleen was not palpable. The blood count on admission was: hemoglobin 9.5 grams, 67 per cent; red blood cells 3,400,000; white blood cells 12,700; neutrophiles 25 per cent, eosinophiles 2 per cent, lymphocytes 72 per cent, monocytes 1 per cent. The clinical diagnosis was pelvic inflammatory disease, gonorrheal arthritis, lymphocytic reaction to sulfonamide medication. Sulfanilamide was given for three days, 15 grains every four hours. On the third day, blood count was: hemoglobin 9 grams, 63 per cent; white blood cells 7,100; neutrophiles 28 per cent, lymphocytes 72 per cent. Blood sulfanilamide 7.8 mg. per cent free, 10.4 mg. per cent total. The fourth day, following a blood transfusion,

* Some of these cases were seen in consultation and the laboratory work which had been done on them was not as complete and in some instances probably not as accurate as would have been desirable.

blood examination showed: hemoglobin 11.9 grams, 83 per cent; red blood cells 3,380,000; white blood cells 3,200; neutrophiles 26 per cent, lymphocytes 69 per cent, eosinophiles 1 per cent, monocytes 4 per cent. Coagulation time was three minutes by capillary tube, bleeding time (Duke), 20 minutes. Just before the sternal puncture was done, with the total counts essentially unchanged, 5 per cent lymphoblasts were noted in the differential: segmented neutrophiles 2 per cent, bands 24 per cent, metamyelocytes 8 per cent, myelocytes 2 per cent, eosinophiles 4 per cent, basophiles 1 per cent, monocytes 4 per cent, lymphocytes 50 per cent, lymphoblasts 5 per cent. Blood platelets were greatly reduced. Sternal puncture revealed a marrow of normal degree of cellularity but 91 per cent of the marrow cells were of the lymphocytic series and 46 per cent of these were lymphoblasts. Diagnosis: Acute lymphatic leukemia in subleukemic phase. Before death the peripheral blood picture became frankly leukemic. The diagnosis was confirmed at autopsy. Sternal puncture of this case during the first hospitalization would probably have indicated the correct diagnosis.

Case 3. A 34-year old white male had been having trouble with aching of his teeth for four months. Three days before admission a swelling developed in the region of the third right lower molar. This ruptured and drained bloody, purulent material. Fever of 101° to 102° F. was present. On admission he showed marked pallor, appeared toxic, and had a necrotic lesion of the right lower jaw. There was slight lymphadenopathy, an enlarged spleen felt three fingers'-breadth below the costal margin, and slight enlargement of the liver.

Blood studies: hemoglobin 7.5 grams, 51 per cent; red blood cells 2,670,000; white blood cells 5,000; segmented neutrophiles 17 per cent, bands 18 per cent, metamyelocytes 3 per cent, myelocytes 3 per cent, eosinophiles 1 per cent, basophiles 1 per cent, lymphocytes 34 per cent, unidentified cells 23 per cent. Three per cent of the latter cells contained nucleoli. With Wright's stain, the unidentified cells seemed to belong to the monocytic group of cells, but with supravital staining they resembled lymphocytes. Moreover, peroxidase staining gave 46 per cent positive and 54 per cent negative, so that no definite conclusion could be reached as to the type of aleukemic leukemia which this patient had. Sternal puncture revealed a marrow of a normal degree of cellularity, but the predominating cell was a myeloblast. All later stages in the development of neutrophiles, eosinophiles and basophiles were present, but in greatly reduced numbers; the red cell line was hyperplastic (myeloid erythroid ratio 1.5:1) and megaloblasts were present, although the majority of the developing red cells were normoblastic. Diagnosis: acute myelogenous leukemia, leukopenic, confirmed at autopsy.

This puncture, though of no practical benefit to the patient, nevertheless gave the correct diagnosis, which could not be made from the peripheral blood.

Case 4. A white male, 70 years of age, had had a resection of his prostate. He continued febrile for eight days, when a scrotal abscess was drained. However, his general condition did not improve and he continued to have fever without obvious cause. During the next eight weeks, his total white blood cell count fell from 21,350 to 5,900 with a marked left shift to 19 per cent myelocytes, and his hemoglobin was 6 grams, 41 per cent and red blood cells 2,140,000. The clinical impression at this time was aleukemic myelogenous leukemia. Sternal puncture showed a hyperplasia of the marrow in the granulocyte series, with a left shift, the dominant cell being a neutrophilic metamyelocyte. Promyelocytes were increased in number, but the percentage of myeloblasts was normal. Red cell formation was below normal. Diagnosis: Leukemoid marrow reaction to infection. *Staphylococcus aureus* was repeatedly isolated from blood culture. He was treated with sulfathiazole and transfusions, and after a month was discharged from the hospital improved. He subsequently developed further localized suppurative infections and granulocytopenia. He recovered and a little over one year later there was no evidence of leukemia.

Case 5. A 38-year-old white male was ill for two months, starting with fever, sore throat and enlarged spleen, which was treated with sulfanilamide, at first with marked improvement. Recurrence with sore throat, fever, and splenomegaly followed, and was complicated by jaundice, pneumonia and anemia. Laboratory data: hemoglobin 10.3 grams, 70 per cent; red blood cells 3,700,000; white blood cells 44,000; 94 per cent large primitive appearing cells considered by another (very well known) laboratory to be indicative of acute leukemia; heterophile antibody test negative. Our differential count on the day of the puncture was: segmented neutrophiles 17 per cent, bands 12 per cent, eosinophiles 2 per cent, basophiles 1 per cent, monocytes 5 per cent, large lymphocytes 3 per cent, intermediate lymphocytes 32 per cent, small lymphocytes 28 per cent. The sternal puncture showed a marrow with a normal degree of cellularity and a normal distribution of cell types except for a marked lymphocytosis. Both in the marrow smears and in the peripheral blood, many of the lymphocytes showed changes which are typical of infectious mononucleosis. No lymphoblasts were seen in any of the marrow smears. Correlation of the marrow findings with the clinical picture indicated a diagnosis of infectious mononucleosis. Complete recovery ensued.

This diagnosis could have been made by further observation and study without puncture, but was made with confidence immediately following this procedure.

Case 6. A white male 44 years of age had been troubled for five months with weakness, general malaise, persistent headaches, and sharp shooting pains in the back and legs. There were periods of remission and exacerbation. His illness had started with chills and fever while working in Panama. This had lasted for four weeks. He had been treated with quinine and neoprontosil. Four blood transfusions had made him feel better temporarily. He had been in two other hospitals for study but was discharged undiagnosed. In this hospital his chief complaints were persistent headaches, weakness and insomnia. Physical examination showed only malnutrition and pallor. Gastrointestinal roentgenographic series and barium enema were negative. Laboratory data: hemoglobin 11.5 grams, 79 per cent; red blood cells 3,260,000; color index 1.2; white blood cells, 8,600; segmented neutrophiles 18 per cent, bands 42 per cent, metamyelocytes 4 per cent, myelocytes 4 per cent, promyelocytes 2 per cent, eosinophiles 1 per cent, basophiles 1 per cent, monocytes 11 per cent, lymphocytes 17 per cent; a few normoblasts were seen in the smear; reticulocyte count 2.7 per cent; sedimentation rate 22 mm. in one hour (Walton), very rapid; non-protein nitrogen 26; gastric analysis following histamine, 0.2 per cent free hydrochloric acid; icterus index 3; serum bilirubin less than 0.5 mg. per cent. No clinical diagnosis could be made. Sternal punctures were done opposite the third, fourth, and fifth costosternal articulations in mid-sternum. In all of them the sternum was penetrated with great difficulty to a depth of at least 1 cm. without encountering a marrow cavity. In the first two no fluid could be aspirated at all, even under strong suction (with a 10 c.c. syringe). In the third a few drops of bloody fluid were obtained which contained fat but very few marrow cells. These consisted of myelocytes and normoblasts which were somewhat less mature than those in the peripheral blood. It was, therefore, suspected that this patient had no marrow cavity in the sternum, and a trephine biopsy was done. (It is interesting to note that under novocaine anesthesia this patient experienced sharp pains which were very disturbing in the three punctures and during the trephining, when the needles and trephine were actually through the periosteum and in the bone itself.) Sections of the trephine biopsy showed heavy bony trabeculae where the marrow cavity should have been. The space between the trabeculae was filled in with fibrous tissue and an eosinophilic mass resembling osteoid tissue. Very small islands of marrow and isolated marrow cells were occasionally present. Diagnosis: osteosclerosis with myelophthisic anemia. Radiographs showed that the skull, pelvis, vertebrae, sternum and shafts of the femora were sclerotic. The blood calcium

was found to be 13.7 mg. per cent; blood phosphorus 3.2 mg. per cent; the phosphatase was 24 Bodansky units. Eight days later repetition of the chemical analyses of the blood showed blood calcium, 9.3 mg. per cent; phosphorus, 4.3 mg. per cent; and phosphatase, 51 Bodansky units. This patient died three weeks later in another city and no autopsy was obtained.

Case 7. A 61-year-old white male complained of abdominal distress of six months' duration. He had attacks of severe pain in the upper abdomen and beneath the sternum which was cramp like and relieved by belching or passing flatus. The attacks lasted several hours, and although they were infrequent at first were now increasingly troublesome. Two weeks before admission his gait had become unsteady. On admission to the hospital he showed marked pallor, an icteric tinge to the sclerae, a normal tongue, a symmetrically enlarged prostate, hypoactive reflexes, vibration sense was normal and Romberg test negative.

Laboratory Data: hemoglobin 6.6 grams, 45 per cent; red blood cells 2,430,000; color index 0.9; white blood cells 3,450; segmented neutrophiles 70 per cent, lymphocytes 29 per cent, monocytes 1 per cent; icterus index 11.4; hematocrit 0.20; reticulocyte count 0.4 per cent; no gastric free hydrochloric acid following histamine; stool negative for occult blood. The day after admission a gastrointestinal series was negative, whereas a barium enema showed an area of constriction at the rectosigmoid. Four days later the barium enema was repeated and showed an area of constriction in the sigmoid colon in which normal mucosal markings were present. The constriction was not constant. Sigmoidoscopic examination was negative. The patient was given ferrous sulphate and his reticulocyte count rose to 1.7 per cent without other improvement. Clinical impression at this time was gastrointestinal malignancy. The day before puncture was done, his hemoglobin was 8.2 grams, 56 per cent; red blood cells 2,310,000; color index 1.2; hematocrit 0.24; mean corpuscular volume 104 cubic micra; mean corpuscular hemoglobin 35 micromicrograms; mean corpuscular hemoglobin concentration 33 per cent. On the thirteenth day after admission a sternal marrow puncture revealed a hyperplastic marrow in which the dominant cell was a polychromatic megaloblast; the red cell line was megaloblastic and hyperplastic and the myeloid-erythroid ratio was 1:2, a reversal of normal; the granulocytic line of cells showed a left shift, with myelocytes predominating; macropolycytes were present in the marrow and the beginning of nuclear deformity could be seen in the myelocyte stage (table 4). Diagnosis: pernicious anemia. The patient was given liver extract parenterally, the reticulocytes rose to 6 per cent on the sixth day subsequently, and he was eventually discharged feeling well, with hemoglobin 10.7 grams, 76 per cent; red blood cells 3,850,000; and color index 1.0. Nine months later, after receiving parenteral liver every two weeks, the hemoglobin was 15.3 grams, 104 per cent; red blood cells 5,100,000.

This case did not show typical blood findings or central nervous system changes which are characteristic of pernicious anemia.* The roentgenographic findings were confusing. It is conceivable that liver therapy might have been tried as a therapeutic test. However, a positive diagnosis was reached quickly by means of the puncture. If this had been done earlier when the etiology of the anemia was first in doubt the period of hospitalization and uncertainty would have been shortened appreciably.

* Since this series of cases was closed, we have seen another case of severe pernicious anemia in a 35-year-old white woman in whom there was also no involvement of the central nervous system and in whom the peripheral blood indicated a hypochromic type of anemia. The laboratory findings on the peripheral blood of this case were: hemoglobin 3.56 grams, 24 per cent; red blood cells 1,400,000; color index 0.8; hematocrit 0.10; mean corpuscular volume 75 cubic micra; mean corpuscular hemoglobin 27 micrograms; mean corpuscular hemoglobin concentration 35.6 per cent. These findings seemed so incredible in view of a diagnosis of pernicious anemia which had been made from sternal puncture that they were repeated twice by each of two observers with identical results. The patient recovered with liver extract therapy. Wintrobe [16] has recently reported two similar cases.

II. Punctures enabling a more rapid diagnosis.

Case 8. A 22-year-old female had been given 10 grains of prontylin (in 1937) every six hours for two days because of a sore throat. Weakness, headache, nausea and vomiting followed. On the fourth day there was a definite jaundice which cleared up on the sixth day. The liver was enlarged. Eight days after the onset of her illness she entered the hospital complaining of weakness, nausea, and vomiting. The patient was extremely pale, underdeveloped and undernourished. There were small palpable lymph nodes in both posterior cervical chains and in the right axilla and inguinal region. The spleen was very firm and palpable one finger's-breadth below the costal margin.

Laboratory data: hemoglobin 2.3 grams, 16 per cent; red blood cells 830,000; white blood cells 17,600; segmented neutrophiles and bands 63 per cent, myelocytes 4 per cent, eosinophiles 5 per cent, basophiles 4 per cent, monocytes 5 per cent, lymphocytes 19 per cent; a few myeloblasts and nucleated red blood cells were present in the smear; reticulocytes 4.5 per cent; icterus index 10; urine negative for bile and urobilinogen normal; the feces contained bile, were negative to the benzidine test, and no ova or parasites were found. The question was whether this was a leukemoid reaction following an acute hemolytic anemia or an acute leukemia. Sternal puncture showed a marrow within the normal range of cellularity, but the predominating cell was a basophilic normoblast. The red cell series was markedly hyperplastic, the myeloid-erythroid ratio being 2:3; a few megaloblasts were seen; the white cell series showed a left shift, but no evidence of leukemia. Diagnosis: leukemoid reaction to acute hemolytic anemia. The patient was transfused and recovered.

This sternal puncture was done the morning after admission to the hospital. All suspicion of a malignant process was dispelled within 24 hours after admission.

Case 9. A 17-year-old white male with a history of epistaxis in childhood three weeks before admission had a nose bleed every one to two days which required packing to stop it. There was occasional nausea and vomiting associated with bleeding. Small purpuric spots had been noted on the forearms for four months. Gingival bleeding and ecchymoses resulted from slight trauma. His father had suffered frequently from epistaxis in childhood. Examination showed a temperature of 100.5° F., pallor, petechiae on the buccal mucosa, liver palpable two fingers'-breadth below the costal margin, spleen not palpable, slight general lymphadenopathy. Laboratory data: hemoglobin 6.5 grams, 44 per cent; red blood cells 2,230,000; color index 1.0; total nucleated cell count 7,400, of which 51 per cent were nucleated red cells, and the white blood cells, therefore, 3,600; segmented neutrophiles 46 per cent, band 7 per cent, metamyelocytes 7 per cent, myelocytes 8 per cent, monocytes 8 per cent, lymphocytes 24 per cent; platelet count 140,000. The red cells in the smear showed anisocytosis, poikilocytosis, basophilic stippling, polychromasia, and many megaloblasts were present as well as normoblasts. Bleeding time was 8.5 minutes; clotting time of venous blood, 6 minutes; no clot retraction; hematocrit 0.19; volume index 1.9; mean corpuscular volume 85.4 cubic micra; mean corpuscular hemoglobin 27 micromicrograms; mean corpuscular hemoglobin concentration 32.5 per cent. Fragility test: hemolysis began at 0.42 per cent and was complete at 0.34 per cent; Rumpel-Leeds test was negative. The clinical impression was purpura hemorrhagica. Sternal puncture was done four days after admission. The marrow revealed markedly increased cellularity with the myeloblast predominating. The neutrophilic series was shifted far to the left with myeloblasts, promyelocytes, and myelocytes present in greatly increased numbers, whereas mature neutrophiles were rare. Red cell formation was increased, the myeloid-erythroid ratio being 1:1. Diagnosis: acute myelogenous leukemia in subleukemic stage. The patient gradually failed and six weeks after puncture the total white cell count rose to 30,000 cells of which 27 per cent were myeloblasts, a

frankly leukemic blood picture. At this stage the patient showed marked gingival swelling so that the teeth were buried in the tissue; the monocyte count rose to 19 per cent. The patient died at home and no autopsy was done.

The correct diagnosis could ultimately have been made in this case without puncture. As a matter of fact, it is felt that sufficiently expert examination of the first blood smear made on this patient would have revealed the nature of his illness. However, under the circumstances, the puncture enabled the consultant to visualize the actual condition of the patient's hematopoietic system, and permitted an earlier diagnosis and a more accurate prognosis than would otherwise have been possible.

III. Punctures confirming diagnosis in doubtful cases.

There were four such cases in our series. In all of them diagnosis was almost certain, and yet there were puzzling features about each case which prevented a definite conclusion. Two of these histories are given.

Case 10. A white male 53 years of age complained of a loss of 35 pounds in six months and a mass in the left upper quadrant of the abdomen, which he noticed himself. Examination showed splenomegaly but no lymphadenopathy and was otherwise entirely negative. Laboratory data: hemoglobin 17.5 grams, 119 per cent; red blood cells 5,940,000; white blood cells 22,400; segmented neutrophiles 21 per cent, monocytes 4 per cent, lymphocytes 75 per cent; platelets were present but reduced in number; the majority of lymphocytes were small and of a mature type. A diagnosis of chronic lymphatic leukemia would have been indicated except for the complete absence of any enlargement of the lymph nodes on repeated examination. Sternal puncture showed a marrow within the normal range of cellularity, but the predominant cell was a small lymphocyte. Both the granulocytic and erythroid series showed all the stages normally found in the marrow in the proper proportion. A differential count of 500 of the marrow cells showed lymphocytes 74.2 per cent, 47.3 per cent of which were small and 26.9 per cent intermediate in size. A few lymphoblasts were seen in the marrow smears during study. Diagnosis: chronic lymphatic leukemia.

Case 11. A 57-year-old white male complained of constipation, loss of weight, anorexia, and discomfort in the lower abdomen for six weeks. For the five days before admission he had had a sore throat and tongue. Examination showed round, elevated white spots over the pharynx, faucial pillars and soft palate; the edges of the tongue were covered with a heavy, white slimy coating, and papillae were absent from the anterior portion. The spleen was palpable, and what was considered to be the liver (see below) was palpable five fingers'-breadth below the costal margin. There was no lymphadenopathy. Laboratory data: hemoglobin 11 grams, 75 per cent; red blood cells 4,500,000; white blood cells 28,500; segmented neutrophiles 75 per cent, bands 14 per cent, metamyelocytes 2 per cent, monocytes 2 per cent, lymphocytes 7 per cent; basal metabolic rate, urine, stool, gastrointestinal series negative; cholelithiasis by roentgenogram; gastric free hydrochloric acid present. Three days later: white blood cells 45,700; segmented neutrophiles 70 per cent, bands 18 per cent, metamyelocytes 3 per cent, myelocytes 2 per cent, monocytes 2 per cent, lymphocytes 5 per cent. A diagnosis of chronic myelogenous leukemia was made but because of the small number of immature cells present in the blood, a leukemoid reaction could not be ruled out. Sternal puncture revealed an extremely cellular marrow (of leukemic degree) in which the neutrophilic band form was the predominant cell but myelocytes and promyelocytes were also greatly increased in proportion to normal. The diagnosis of chronic myelogenous leukemia was confirmed. The patient was discharged from the hospital, but returned again four weeks later with a red blood count of only 2,700,000; the total white blood count remained the same as before.

but 5 per cent myeloblasts were now present in the peripheral blood. One week after the second admission, the patient died, and at autopsy it was found that the mass in the right upper quadrant was not liver but a large hypernephroma which, however, had not yet metastasized. The bone marrow and the spleen showed changes typical of myelogenous leukemia, but no leukemic infiltrations were found in any other organ.

IV. Punctures aiding differential diagnosis.

Twenty-six of our 74 cases in which there was a clinical indication for doing the puncture fall into this category, as they showed non-specific myelograms. Although a diagnosis usually cannot be made from punctures which give negative results, they are in many instances of help in differential diagnosis, and may present certain information which cannot be obtained in any other way. Too much reliance should not be placed on them, the results must be interpreted guardedly and only in relation to the general clinical picture. The usefulness of the method in differential diagnosis is shown in the following five cases.

Case 12. A 57-year-old white male had had a resection of a carcinoma of the ascending colon. Five days after operation purpuric spots on the skin, epistaxis and melena appeared, and were accompanied by pallor. Laboratory data: hemoglobin 4.3 grams, 29 per cent; red blood cells 1,380,000; white blood cells 4,640; segmented neutrophiles 35 per cent, bands 23 per cent, metamyelocytes 2 per cent, eosinophiles 3 per cent, monocytes 11 per cent, lymphocytes 26 per cent; platelets, 31,000; bleeding time, 25 minutes; coagulation time, 12 minutes (venous blood); no clot retraction in 24 hours; reticulocyte count 1 per cent. Purpura hemorrhagica was strongly suspected by the surgeon who considered the advisability of doing a splenectomy. Sternal puncture showed an almost complete absence of marrow cells, although marrow fluid was obtained easily. This fact tended to rule out purpura hemorrhagica, because in this disease marrow findings are essentially normal, and suggested that an aplasia of the marrow was present. A trephine biopsy of the marrow would have been done except for the critical condition of the patient. By deduction it was felt that the most logical cause for marrow aplasia in this patient was metastatic carcinoma. Autopsy of this case showed widespread carcinomatosis with replacement of marrow tissue. It is interesting that with such metastases present no malignant cells were found in the fluid obtained by puncture.

Case 13. A white male 33 years of age had a marked hypochromic anemia for which no cause could be discovered. A sternal puncture was requested for added information because the etiology of the anemia could not be determined. Sternal puncture showed hyperplasia of the red cell series in a marrow with a normal degree of cellularity. A diagnosis of iron deficiency anemia was made and iron therapy was carried out successfully with assurance that the more malignant diseases considered were not present.

Case 14. A 21-year-old white male had suffered from a condition diagnosed twice as infectious mononucleosis, for a period of three years, with only short periods of well-being. He again showed lymphadenopathy and a typical blood picture of mononucleosis. Since no case of this disease had been reported lasting for such a long time, it was felt that lymphatic leukemia had to be considered. The sternal marrow, though of increased cellularity, was normal cytologically, so that a diagnosis of chronic lymphatic leukemia was not supported.

Case 15. An 80-year-old white female had enlarged non-tender lymph nodes in the left neck, both axillae and both inguinal regions. The liver and spleen were definitely palpable one finger's-breadth and two fingers'-breadth below the costal margin respectively. There was a definite but moderate hypochromic anemia but the total white blood cell count was normal and no immature cells were present. The sternal marrow was normal except for a slight lymphocytosis. It was then felt that lymphatic leukemia was probably not present. Biopsy of a gland was not desired in this patient by the attending physician so roentgen-ray therapy was advised. Marked temporary improvement occurred with this treatment.

Case 16. A white male 64 years of age was found to have anemia but nothing abnormal in his white cell count, after an enlarged spleen palpable three centimeters below the costal margin was discovered. He had been chronically fatigued, and felt continually sleepy for one and a half years. For two months he had had lower abdominal pains but gastrointestinal roentgenograms were negative. A history of habitual use of Bromo-Seltzer over a period of four to five years was obtained. Undernutrition and a dusky pallor with a cyanotic tinge to the mucous membranes were noted. The blood bromides were over 100 mg. per cent, with no methemoglobin present. The attending physician's impression was aleukemic leukemia. Sternal puncture showed a normal cellularity in the smears, with some left shift in the neutrophilic series, the predominating cell being, however, the band form. The diagnosis was chronic acetanilid and bromide intoxication with splenomegaly. The sternal marrow examination was felt to be of definite aid in the differential diagnosis of this case.

TABLE IV

Form Used in Making Reports on Sternal Punctures

ALBANY HOSPITAL
MYELOGRAM

Name: Doe, John
Hosp. No. 55,963

Date: June 18, 1940

Findings	Normal Marrow	Patient's Marrow
Cellularity	Grade 1, 2, or 3 (usually 2)	Grade 3
Predominant Cell	Segmented or band neutrophile	Polychromatophilic megaloblast
Neutrophilic Series	Complete series; few early forms	Shifted to left, myelocytes predominating
Erythroid Series	Normoblastic; few early forms	Megaloblastic hyperplasia; many early forms; normoblasts scanty
Myeloid-Erythroid Ratio	3 : 1 to 50 : 1	1 : 2
Reticulocyte Count	0.5% to 4.0%	1%
Lymphocytic Series	Small number of mature forms	Normal
Monocytic Series	Small number	Normal
Other Cells	Small numbers of plasma cells, megakaryocytes, reticulum cells, macrophages, cells in mitosis, eosinophiles, basophiles	Macropolycytes present

Discussion:

This marrow is almost completely megaloblastic. The myeloid-erythroid ratio is reversed, indicating a marked hyperplasia of the erythroid elements. The beginning of nuclear deformity resulting in the formation of macropolycytes can be seen in the myelocyte stage.

Diagnosis: Megaloblastic marrow typical of pernicious anemia in relapse.

Myelogram

The results of the sternal punctures are reported by a form (table 4) called a "myelogram," which is in essence a brief tabulated description of the marrow picture compared to normal marrow. In our experience, this form of report is much more satisfactory than a differential count or a cytological description of the puncture findings, as both the count and the description are unintelligible to persons not particularly interested in hematology. Total and differential counts of marrow cells in the puncture fluid are not essential for practical interpretation, although occasionally a differential count is necessary for the purpose of establishing the predominant cell type. The facts on which the normal myelogram is based have been already discussed in the section on cytology.

In studying the literature, as well as our own data, it became at once apparent that sternal puncture findings fall into two groups: (1) myelograms which are typical of a particular disease, and which when present are so reliable as to either indicate the diagnosis or to be actually pathognomonic. These may be termed specific or typical myelograms; (2) myelograms which are non-specific and which may occur in a variety of conditions and be useful in association with the complete clinical picture, but which alone are without value for diagnostic purposes. Specific myelograms are present in the following conditions:

1. Leukemia, especially acute and leukopenic leukemia.
2. Megaloblastic marrow, present typically in pernicious anemia in relapse, achrestic anemia, and sprue.
3. Agranulocytosis in the arrested marrow stage.
4. Neoplasms: multiple myeloma and metastatic malignancies, especially carcinoma.
5. Lipoid histiocytosis.
6. Malaria.
7. Leishmaniasis (kala azar).

It is not to be assumed that all of the above conditions will always give diagnostic marrow pictures, but when specific findings are present they indicate the diagnosis. Bizarre cases are encountered in which the picture is doubtful, confusing, or possibly even negative. The absence of a typical myelogram cannot be relied upon absolutely to rule out a disease in differential diagnosis, because of the possibility of an error in sampling and atypical variations in pathology. Negative findings can, however, be extremely useful in some instances, as is shown by cases 5, 13, 14, and 16 of this paper.

In chronic myeloid leukemias, the peripheral blood findings are usually adequate for diagnosis without investigation of the marrow. Sternal puncture is, however, indicated in cases of chronic leukemia in a leukopenic phase, in early cases in which peripheral blood studies are inconclusive, and in cer-

tain cases in which conflicting data throw doubt on the diagnosis. Incontestable evidence of myeloid hyperplasia is, however, necessary for a diagnosis when the peripheral blood picture is not characteristic, and there must be a marked increase in the younger types of cells, namely the myelocytes, promyelocytes, and myeloblasts. These marrows are usually of Grade 4 cellularity. Eosinophilic and basophilic myelocytes and promyelocytes may also be markedly increased over normal.

Large numbers of myeloblasts, with either this cell or the promyelocyte as the predominating type, are necessary for a diagnosis of acute myelogenous leukemia. The designation of an arbitrary fixed percentage of a cell type above which leukemia is stated to be present, as has been suggested by some authors, seems to us in the present state of knowledge extremely unwarranted.

In chronic lymphatic leukemia the bone marrow is replaced by lymphatic tissue, and most of the cells seen in the puncture fluid are of the mature type, though occasional lymphoblasts are present. In acute lymphatic leukemia, however, lymphoblasts are the predominating cells. This transformation of the marrow may occur with a leukopenic peripheral blood picture. In certain other diseases, such as infectious mononucleosis, there is a relatively high percentage of lymphocytes in the peripheral blood, and accordingly a relatively high lymphocyte count will occur in the marrow, but the marrow is obviously not being replaced by lymphocytes.

In acute monocytic leukemia the normal marrow is replaced by monocytic cells and large numbers of premonocytes and monoblasts are found. This may also occur when the peripheral blood picture is leukopenic.

It must be borne in mind that accompanying the conditions which produce leukemoid reactions in the peripheral blood, such as infection, acute hemolysis and acute hemorrhage, a hyperplasia and a "left shift" of the leukocytes may occur in the bone marrow. As a matter of fact, the peripheral blood picture is merely a reflection of the change in the marrow. The percentage of younger forms of the neutrophilic series increases, but the increase is mostly in the bands and metamyelocytes, and the myeloblasts are not affected in the small number of cases we have examined. Sometimes, however, a leukocytosis does not occur in the peripheral blood and the "left shift" may be present in spite of the leukopenia. It is felt that under these circumstances although the marrow is hyperplastic, delivery of cells to the peripheral blood is defective. The eosinophilic marrow cells are not affected unless an eosinophilic leukocytosis is also present in the peripheral blood.

In agranulocytosis, two types of marrow may be found: (1) the more mature forms of the neutrophilic series are absent, which may be a "maturation arrest," but all the younger forms are present and may even be increased in number; and (2) a so-called "empty" marrow in which all granulocytic cells are absent and only lymphocytes, plasma cells and small normoblasts are present in the smears. In the latter type, in some cases, very few cells of any

kind are present in the smears. Curiously, in three of the five cases of this disease we studied the erythroid series was represented only by small normoblasts. The significance of this is not evident. In our small series of cases, a "maturation arrest" of the marrow was indicative of a more favorable prognosis. In empty marrows, the prognosis was bad. A "maturation arrest" in the marrow is a typical myelogram, and is diagnostic, but in the marrows showing a complete absence of granulocytic cells a trephine biopsy must be done to avoid confusion with true aplastic anemia and myelophthisic conditions, or the diagnosis must be based on the associated clinical picture, which is not always reliable.

The recognition of megaloblastic marrow is of great importance in the diagnosis of pernicious anemia. The presence of megaloblastic cells in a case of anemia, without other explanation for the anemia (such as leukemia or sprue) and in the presence of true achlorhydria is sufficiently diagnostic of pernicious anemia to indicate a therapeutic test with a large dosage of liver extract, even though the peripheral blood studies are inconclusive. The marrow findings are identical in pernicious anemia and sprue, but the latter disease is of course characterized by a quite different clinical picture. These two diseases, in addition to the abnormal variety of red cells, also have pathological changes in the neutrophile series. These consist of abnormally early maturation changes in the nucleus, so that it is possible to find promyelocytes which have the nuclear characteristics of band forms.[7] The continuation of these changes results in the formation of the "hypersegmented pernicious anemia neutrophile" or macropolycyte, which is sometimes found in the peripheral blood and which may have as many as 15 lobes in the segmented nucleus. Following the injection of liver extract, as is well known, the bone marrow and the peripheral blood return to normal. The beginning of the transformation may be apparent in the marrow 12 hours after injection, it is said. The change is accomplished by the rapid maturation of the megaloblastic cells to non-nucleated megalocytes; they are replaced in the marrow by normoblastic cells which then mature to normocytes, and it is only at this time that the Price-Jones curve returns to normal. There is no evidence that megaloblastic cells ever transform to normoblasts. The abnormal neutrophilic cells mature and are replaced by normal cells in some but not in all cases. Achrestic anemia also has a predominantly megaloblastic marrow, and the peripheral blood picture may be identical with pernicious anemia but free hydrochloric acid is secreted by the stomach and proper response to liver extract does not occur. Megaloblasts in smaller numbers were also found in other conditions in our series of cases: in leukemia, acute hemolytic anemia, and in one clinically typical case of acute "aplastic" anemia in a young adult. In these latter conditions, however, the normoblastic type of erythropoiesis was the predominant form of red cell production.

In our cases, neoplasms have been studied only as they have entered into

the differential diagnosis of hematological disorders. It is felt that other methods of investigation are superior to sternal puncture in diagnosing malignancies, with the exception of multiple myeloma. No tumor cells were found in the puncture fluid in any of our cases, except in our one case of the latter disease.

In the one case of lipoid histiocytosis which we were able to study, no foam cells were found in the puncture fluid. They were found, however, in a biopsied lymph node. This case illustrated the dangers of ruling out a disease because of negative puncture findings.

Malaria and kala-azar have not occurred among the cases we were able to study. They are listed among the specific myelograms because other investigators have shown that sternal puncture is often of help in their diagnosis. Sternal marrow, obtained by trephine, was first used in the diagnosis of the latter two diseases by Seyfarth.[17] In kala-azar, sternal puncture is preferred to splenic puncture as it is less dangerous to the patient. Not all of the investigators of the question are in agreement, but it is said that malaria can be diagnosed from sternal puncture samples when the peripheral blood is negative, a finding which may be of importance in tropical medicine.

All other diseases so far studied have a nonspecific marrow picture. The nontypical or nonspecific myelograms, though they do not give the diagnosis, are often of great interest and usefulness in relation to the general clinical picture. Polycythemia, hypochromic, hemolytic and aplastic anemias, and myelophthisic anemia such as occurs in Hodgkin's disease and reticulosis, are among the diseases giving marrow pictures which are not diagnostic. Aplastic anemia is placed in this category because it may show a marrow condition upon puncture which varies from complete aplasia to extreme hyperplasia. One of the cases of this disease which we studied was a clinically typical case of acute idiopathic "aplastic" anemia in a young adult, but the marrow was of normal cellularity with a normal myeloid-erythroid ratio; there was a left shift in the neutrophilic series and also in the erythroid series, and some megaloblastic red cell formation was present. The presence of megaloblastic cells in this marrow is of considerable scientific interest, as it has been previously reported [8, 15] that megaloblasts do not occur in this type of case. In the true aplastic anemias, such as our second case of this disease, complete aplasia of the marrow is present, but a trephine biopsy is necessary after the sternal puncture has been done in order to be sure that the failure to aspirate any cells is not due to a replacement process which resists aspiration.

Clinical Indications for Sternal Puncture

After a thorough examination of the case histories and the evaluation of the results of the punctures in our series, the following criteria were selected as indications for the practical use of the sternal puncture method

of marrow biopsy. A sternal puncture should always be done when (1) the diagnosis is in doubt and a disease usually showing a typical myelogram cannot be excluded, for example, an agranulocytosis in which there is the possibility of aleukemic leukemia; (2) the etiology of the peripheral blood findings is obscure: "aplastic" anemia or "idiopathic" anemia; (3) other means of diagnosis short of surgical biopsy have failed. In addition, a sternal puncture *may* be done to (1) save time if a specific marrow picture is likely to be present; (2) obtain information concerning prognosis; (3) determine response to treatment, as in a pernicious anemia which does not seem to benefit from liver extract therapy; (4) determine the type of a "stem cell" leukemia when this cannot be done with certainty from the peripheral blood.

Conclusions

We find that sternal puncture, when used on cases in which it is definitely indicated, is an extremely valuable and practical diagnostic method. Elaborate technics of handling and studying the marrow samples, however valuable from a research standpoint, are unnecessary for clinical use of the method. Under actual working conditions 65 per cent of our indicated punctures gave information which was of clinical value, and the diagnosis was made by means of the puncture in 16.2 per cent of our 74 indicated cases. Sternal puncture cannot be substituted for thorough clinical investigation of the patient. Indeed, the more thorough the work-up of the patient, the easier and more valuable is the interpretation of the puncture. Most diseases, unfortunately, do not show specific changes in the marrow from which a definite diagnosis can be made, but much clinically valuable information can be obtained which is of aid in the differential diagnosis and subsequent handling of the patient. Diagnoses should be made only from specific myelograms, and a negative result does not absolutely preclude the presence of a given disease, because of the possibility of not having secured a representative sample of marrow and of atypical variations in the pathologic lesions of the disease. Punctures which yield no marrow cells upon aspiration should be followed by a trephine biopsy, if the diagnosis can be reached in no other way, and no contraindication is present.

Summary

1. Sternal marrow puncture is an extremely useful and practical procedure in the study of diseases of the blood and in cases in which the possibility of such diseases enters into the differential diagnosis. It should, however, be used only on definite indications.

2. In our series of 140 cases, 65 per cent of the 74 indicated punctures gave information of clinical value, and the actual diagnosis was made in 16.2 per cent when this was impossible by any other method short of biopsy.

3. Diagnosis can be made with certainty only when a typical or specific myelogram is present.

4. Negative findings must be interpreted with caution and fully correlated with the entire clinical picture.

5. No diagnosis can be made from nonspecific myelograms, but they sometimes yield information of great clinical value.

6. Sternal punctures may also be clinically useful for rapid diagnosis, confirmation, prognosis and for follow-up of treatment.

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KALA AZAR: A REVIEW OF ITS INCIDENCE AND EPIDEMIOLOGY IN CHINA AND CLINICAL OBSERVATIONS ON 585 CASES *

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THIS paper has chiefly a threefold purpose: to report chronologically on the incidence of kala azar in China, to present an up-to-date summary of what has been done in China to determine how this disease is spread, and to offer a study of some of the cases seen by us by presenting tables and observations dealing with symptoms, physical signs, laboratory data and responses to therapy.

HISTORY

There are no records or descriptions of a clinical syndrome resembling kala azar in old Chinese literature, as is the case with malaria.† It is therefore impossible to determine how long the disease has existed in this country. If the presence of enlarged spleens in children can be interpreted as evidence, it was present for many decades before its identity was determined.

Very little is known regarding the time and mode of ingress of kala azar into China. Two possible routes of entry have been suggested. One is by way of trade routes from India across the Himalaya mountains and north through Tibet. The other is by sea, also probably from India. The port of Haichow, which has been an important trading center for many years, could reasonably be considered as a portal of entry and source for the infection of the districts where kala azar is most prevalent.

DISTRIBUTION

Kala azar is endemic throughout the whole of China north of the Yangtze River, extending west to Szechuan and north to Manchuria. However, it is most prevalent in Hopei, Manchuria, Anhwei and Kiangsu along the old Yellow River bed. A total of 5,000 cases was treated annually in three hospitals in this last area. Sporadic cases are only occasionally reported in southern China.

Our earliest record is from a letter by Rev. J. S. McIlvaine written from Tsining, Shantung, on February 26, 1880 which reads, "A few days since I was applied to in regard to a case of 'pe' (spleen), a common disease here, which I cannot make out in

* This article was received for publication October 31, 1941, but its appearance was delayed because of the protracted internment of the author in China by the Japanese. Since his release and return to the United States in December 1943, the article has been revised to give consideration to more recent discoveries, particularly regarding the mode of transmission of the disease.

From the Bachman Hunter Memorial Hospital, Tsining, Shantung, China, of which the author was superintendent.

† From a personal letter from Dr. Hoeppli of Peiping Union Medical College.

Flint's Medicine. It is a hard growth which gradually extends over the whole abdomen. They say there is no liquid effusion. . . . The bowels are not interfered with nor is there pain, but when the abdomen is all hardened the person dies." *

In 1887 and 1888 Coltman [1] reported cases of enlarged spleen seen in the Tsinan, Shantung, dispensary. It was refractory to all forms of attempted treatment. The patients also exhibited "pearly conjunctiva, pale flabby tongue, gradual loss of flesh

FIG. 1.

and ultimate death." The first two cases of kala azar recognized in China were in a German soldier who died of it in Peiping in 1900 and in a native from Hankow in 1905. Young [2] mentioned these, and in addition subsequent cases in Tsingtao, Tientsin and Kiukiang, all seen before 1910.

In 1911 Aspland [3] reported from Peiping that kala azar was frequently encountered in the northern provinces, but occurred only in children. Jeffrys and Maxwell [4] stated that in 1911 it was common over the greater part of China north of the Yangtze River and the provinces on the south, but absent farther south. Also in 1911 and 1912 Cochran [5, 6] described the disease in 12 centers in north China and reported a number of infections in children whose disease had been diagnosed by

* Taken from "On the Shantung Front"—J. J. Heeren, p. 204.

liver and spleen punctures. Reed [7] reported a case from Ch'angsha the following year, and mentioned that it seemed to have been contracted from the bites of bedbugs. Wylie [8] observed 35 in-patients in Paoting, Hopei, from 1919–1920. Most of them came from the flooded districts in the southeast.

Young [2] in 1923 reported a total of 25 kala azar areas, adding 13 to those already mentioned by Cochran. A Weihsien report [9, 10] states that in 1922 and 1923 kala azar was prevalent in east central Shantung, although recently its incidence has decreased. King [11] found it in Kansu. Taylor [12, 13] reported an average of 9 to 10 cases a year in Mukden from 1917 to 1931, coming from districts 200 miles west and 100 miles southwest, as well as from Shantung. Morris [14] reported a case from a district in Kiangsu where the disease had not been encountered previously. Also in 1931 Sturton [15] found it in Chekiang. Two years later [16] it was identified in Kiangsi, spreading north along the Tsinpu R. R. and opening up a new area (Nanchuang) where it had become epidemic. In Chinchiang 5,000 cases were seen from April 1932 to April 1933. From here it extended south.

In 1934 Fan and Scott [17] reported 302 kala azar cases among 5,800 in-patients in Tsinan, Shantung, 57 of whom had noma. Du and Best [18] gave a case report on a patient seen in Kansu two years later. Schretzenmayr, Chu and Tsen found 84 cases in Canton in 1938. Nearly all of these were soldiers or officers, and it seemed that they had contracted the infection in the north.[18] Clow [19] in 1941 found 196 cases in Sian, Shensi, 93 per cent of which were infected locally.

Many Chinese have asserted that kala azar follows in the wake of famine, flood and war. These observations are borne out by its prevalence in the north of China between Nanking and Peiping where almost from time immemorial one catastrophe after another has repeatedly ravaged the country. Wylie [8] reported that his 35 patients came from flooded districts. A review of the literature on the incidence of kala azar in north China was made in 1942 and 1943, and it revealed that there had been a marked increase since the outbreak of Japanese hostilities. But it is practically unknown in the south of China where crops are a surer venture and where wars do not so frequently penetrate. However, its infrequency may be due to the absence of the transmitting vector, or reservoir host.

In our district of southern Shantung kala azar remained endemic until the end of 1937. Prior to this we rarely saw more than 8 cases a year, although 110 miles to the east a hospital had continually been having large clinics since its opening several decades ago. Then after the onset of the Japanese invasion the number of our cases suddenly increased.

Incidence

Although kala azar frequently does occur in the cities it is usually a disease of the villages. Many families will often have one courtyard, but usually there will be only one case present. However occasionally we found more than one patient in a family. In the larger cities it is usually found only in the outskirts where the sandfly exists. In general it is a disease of the poorer classes, but this is probably due to the location of their abodes rather than to social status.

"The number of cases presenting themselves for treatment is not only dependent upon the incidence of the disease in the community, but is also influenced by the efficacy of the therapeutic agent, the price of the treatment and the accessibility of the hospital." *

The 585 patients reported in this article were seen from January 1, 1940 to June 30, 1941 and included both in-patients and out-patients. The incidence of the disease by age and sex is recorded in table 1 and corresponds

TABLE I
Age and Sex

	1–2	3–5	6–10	11–15	16–20	21–25	26–30	31–40	41–50	over	Total
M	6	55	152	116	76	48	30	39	8	0	530
F	4	5	13	18	3	4	3	3	2	0	55
Total	10	60	165	134	79	52	33	42	10	0	585

to the observations of others. Perhaps there is a higher incidence above the age of 20 than is usually noted. The low proportion of female patients is of interest merely in demonstrating a preference for first treating the opposite sex. Therefore it is of no scientific interest, as an accurate record of the comparative incidence of the disease in the two sexes could be obtained only by a house to house canvass in the infested villages.

A record was made of the estimated month of onset in 488 patients. The others were excluded either because of a long illness with an indefinite history, or because of the fact that the disease began gradually with no recognizable time of onset. In such cases the enlarged spleen was the first sign of the disease. In spite of the probable errors, in view of the number of patients reported, it might be expected that if there was a seasonal variation in the incidence of the disease it would be reflected in the general trend of estimated months of onset; that is, provided there was not too great a variation in the incubation period. This has been estimated as ranging from two to 16 weeks. In this case a drop in the incidence of the disease would be expected four months after the suspected vector had ceased to be prevalent. This seemed to be borne out by the observations of Yuan et al.,[20] which will be mentioned shortly. However, our record revealed a fair degree of uniformity for all the months of the year. This was even more obvious if a leeway of a month, more or less, was allowed in either direction. This observation would not seem to support the theory of the sandfly as a vector, because those species in which flagellates develop become rare in July and August and practically extinct in September. If this theory is correct a drop in the incidence of onset would be expected some four months after August, as was discovered by Yuan.

In 1939 Yuan, Chu and Lee [20] reported a series of 36 infants with kala azar in the first year of life as seen in the Peiping Union Medical College

* From a personal message from Dr. T. Yates, formerly of Hwaiyuan, Anhwei.

These were studied with reference to the estimated month of onset of the first symptoms as related to the month of birth. They found that allowing for a variable incubation period, in most cases the infection began in early summer, May 15 to July 15. This corresponded to the prevalence of *Phlebotomus chinensis,* the only sandfly so far known in China which can carry flagellates in its intestinal tract in the absence of gross blood, and also have them in its mouth parts. These infants had no chance of previous infection. Yuan emphasized that these data are more significant in infants than those on adults which are more variable and less reliable.

Epidemiology

Although it has been known for a long time that kala azar is a communicable disease, it is only recently that proof of how it is transmitted has been obtained. A complete review of the work done on this problem would be impossible, so only a few of its high lights will be presented. Adler and Theodor [21] demonstrated the infection in dogs and in *Phlebotomus perniciosus* in the Mediterranean region. The work of Shortt and others in India from 1926 to 1932 has contributed a firm foundation to the present knowledge of sandfly dissemination and hamster inoculation. An interesting record of much of the research work on the epidemiology of kala azar is given in outline form by Forkner and Zia,[22] bringing it up to 1934. We shall review the work done on the problem in China in the Peiping Union Medical College, and only a few references will be made concerning other investigations.

Research on the epidemiology is hinged around two theories: the indirect and direct methods of transmission. The former is the one which has generally been favored by most investigators. In India, Shortt and others have developed the theory of a person to person spread through the sandfly as vector, whereas in the Mediterranean countries Adler with others has supported the theory of a canine host supplying sandflies with parasites, with subsequent infection of man by the infected flies. It is this theory which is now being studied in China. Chinese hamsters which are more susceptible than man are used in the experiments.

Theory for the Indirect Transmission of Kala Azar

Sandflies were first suspected of being a possible vector by Pressat in 1905. Since that time flagellates have been found in bedbugs, fleas, lice and mosquitoes,[22] but as the parasites soon die out these have not been considered seriously as possible vectors.

Although canine leishmaniasis was recognized over a decade ago in the Mediterranean region by Adler, it was not found in China until 1934.[23] Lee [24] three years later found two dogs similarly infected. One of these was in a household where a child had kala azar. Only a few cases of canine leishmaniasis have been found in India in spite of the prevalence of human infection. (The disease in the dog is easily identified by the skin lesions which first appear around the eyes and at the base of the ears. They consist of the following signs in sequence of development: seborrhea, scaling, depillation, thickening, nodule formation and ulceration.[25])

The work of Napier [26] showed that *Phlebotomus argentipes* was present only in kala azar endemic areas and that the prevalence of the disease corresponded with the sandfly incidence curve, allowing for a three to four month incubation period. In 1938 Wu and Sung [27] reviewed the work of previous investigators which showed that (1) Leishman-Donovan bodies undergo development in *Phlebotomus argentipes*, and that these are able to infect hamsters by their bite (Shortt et al., 1926 and 1931, and Napier, 1933); (2) *Phlebotomus chinensis* became infected from hamsters with kala azar (Young and Hertig, 1926); and (3) in 1935 flagellates were found in 5 per cent of the sandflies which had fed on patients. Wu and Sung allowed erect haired sandflies (*P. chinensis* and *sergenti*) to feed on patients and hamsters with kala azar. More flagellates were found in those flies which had fed on hamsters, probably because more parasites were available in the skin. Also more flagellates were found in *P. chinensis*, possibly because of a more suitable pH in the gut. They concluded that in this fly there was a tendency to a forward extension into the proventriculus, flagellates remaining motile four to six days after feeding. Feng and Chung [28, 29] in 1939 corroborated these findings after observing sandflies (*P. sergenti* and *chinensis*) artificially infected from four diseased dogs. Therefore *P. chinensis* was found to be the better host as it could maintain an active infestation. Chung et al.[30] examined 587 apparently normal dogs and found leishmania in the viscera of 1.4 per cent.

Hoeppli [31] in a review of the epidemiology mentioned that direct transmission was not an important consideration as the parasites died in the feces, urine and oral (or nasal) secretions when dry. He referred to the investigation of Chung and Wang [32] who showed that intraperitoneally infected hamsters cured of *Leishmania donovani* with neostibosan were immune from inoculations of *L. canis*. From this it was inferred that the two diseases might be identical, and that *P. chinensis* passed it from dog to man. In 1940 Chung,[33] continuing the study of the relationship between human and canine kala azar and between *L. donovani* and *L. canis*, noted that dogs might constantly be a source of infection and that all infected dogs had passed through at least two sandfly seasons. Chung and Feng [34] found visceral lesions in a hamster which had received an intraperitoneal injection of the saline suspension of parasites from *P. chinensis* which had fed on an infected dog.

Until recently (in China) only these two erect haired types of *Phlebotomus* (*P. chinensis* and *sergenti*) have been found capable of carrying parasites. However in 1938 Yao and Wu [35] found a new form of erect haired fly and suggested the name *P. kiangsuensis* as it was found in Chingchiang, Ku. Later the same observers [36] reported the presence of *P. barraudi*, another erect haired type, in Yunnan. Later these may also be shown to be carriers of flagellates.

What may prove to be the last link in the chain of evidence incriminating the sandfly as the vector of kala azar was forged by Swanmath, Shortt and Anderson in 1942.[37] These investigators were able to infect man through the bites of *P. argentipes* which had fed on a patient with leishmaniasis. They attributed their success to the fact that after infection the flies were fed on raisin juice rather than blood, which was the food used by other investigators who had failed in demonstrating this vital step. No reason can yet be offered why raisin juice seemed the cause of their success. Although this may not be the final proof of the epidemiology of the disease, it would seem that if this work is supported by others it is indeed the beginning of the final chapter.

Theory for the Direct Transmission of Kala Azar

This rests on the presumptive evidence that Leishman-Donovan bodies which were obtained from tonsillar and nasal secretions, caused an infection when injected intraperitoneally into hamsters.[22] From this it is concluded that the disease can be

conveyed by Leishman-Donovan bodies as well as by the flagellate form of the parasite. Hamster infection was similarly brought about by the injection of urine and prostatic fluid of patients with kala azar.[38]

Summary

The evidence supporting the indirect transmission theory rests primarily upon: (1) the finding of the flagellate form in the sandfly; (2) the susceptibility of the sandfly to infection by feeding on patients, hamsters and dogs with kala azar; (3) the ability of the sandfly to infect hamsters; (4) the presence of parasites in *P. chinensis* after the disappearance of blood from the gut, and their forward extension into the proboscis; and (5) the transmission of the disease to healthy adults through the bites of sandflies which had fed on a patient with kala azar. It is supported secondarily by the apparent similarity between the canine and human infection, as shown by similar immune reactions to both types in hamsters.

Direct transmission would seem a simpler solution, but the argument against it lies in the early death of the parasite when dried. Therefore if this is the only means of spread, all cases must have been exposed directly to an infected individual, or to their moist secretions.

Serology

Chung and Lu [39] carried out complement fixation reactions with the serum of patients, dogs and rabbits with kala azar against antigens of *L. canis* and *L. donovani*. Practically identical reactions occurred in each instance. They suggest that dissimilar results in previous reports are due to faulty technic, or a difference in antigen preparation.

Pathology

Assuming the sandfly is the vector, the first stage of the disease is the implantation of the flagellates into the skin. From here they are carried to the lymph node of that particular region, where they multiply as Leishman-Donovan bodies throughout the incubation period. Finally the lymph node is no longer able to contain them, and they break through their local confines, entering the blood stream. (No doubt it is this incident which is the cause of primary fever and chill.) The circulating parasites are removed by the reticulo-endothelial cells wherein they multiply until the cell is ruptured. Mononuclears, clasmatocytes and leukocytes also serve in removing the parasites from the blood stream.

The reaction of the cells to this process determines the pathological picture. In the spleen there is a distention of interlobar capillaries, a proliferation of parasitized cells and an increase of connective tissue. Hu [40] described a decrease in the number of parasites accompanying treatment or complications. He also mentioned that there is an enlargement of the liver with parasites in the Kupffer and hepatic cells resulting in atrophy and cir-

rhosis. (This may account for ascites in some chronic cases.—Author.) Hu stated that the bone marrow is hyperplastic, and contains parasitized reticulo-endothelial phagocytes. He found that under treatment the parasites disappear more slowly than from the liver and spleen. Parasites are also found in the lymph nodes, in the alveolar wall cells, in the skin about the sweat glands and blood vessels, in the intestinal submucosa and in the testes and kidney.

Pai and Hu [41] studied the possibility of a leukolysin in the serum of patients, and first presented the following theories for leukopenia: (1) a displacement of normal myeloid tissue by parasitized reticulo-endothelial cells, (2) a failure of myelocytes to maturate, or (3) a destruction of leukocytes by a lysin thrown out by the parasites.

Wang [42] in a histopathological study of the spleens of hamsters with kala azar undergoing treatment with neostibosan described three stages. The first, or proliferative stage, consists of an increase in plasma cells and lymphocytes resulting in a segregation of parasitized reticulo-endothelial cells. The second, or stage of resolution, is identified by degeneration, disintegration, or atrophy of reticulo-endothelial cells with a disappearance of the parasites and nuclei. As the plasma cells decrease the lymphocytes increase. The third stage is that of repair, with a decrease in lymphocytes and an increase in fibroblasts. The final stage may be lymphocytic, proliferative, fibroblastic, fibrotic, or a return to normal. Clinical observations would seem to support a similar process in man.

Symptoms

Although the incubation period is presumed to range from a few weeks to four months, without knowing the actual means of infection this has been entirely presumptive. The symptoms will be discussed separately in order of importance. The first is fever which probably marks the onset of the disease in each case, although it may not be recognized. Its first rise often resembles that in malaria wherein a chill is followed by severe transitory pyrexia. It is possible that this occurs when the parasites are in the circulation, and when they would be found in blood smears. The malarial-like chills recur only a few times and are not usually experienced again. After this the fever is rarely continuous, but comes and goes in periods of varying length. Very often it will be described as being present in either the first or second half of each month. The appetite is poor during pyrexia, but at other times is quite normal.

Enlargement of the spleen is almost universal. It usually becomes noticeable within two or three months after the first attack of fever, and often much earlier. In children it enlarges much more rapidly, often reaching into the pelvis in the course of a few months. In adults this rarely occurs; in fact it seems to reach a standstill after varying periods and does not enlarge further although the disease remains untreated. In such

instances it may become firmer than at first. It seems to cause no particular discomfort even when it has reached huge proportions and may result only in tympanites. We have not noticed an enlarged liver in most of our cases, as is so frequently mentioned by other observers.

Shortly after the onset of the disease all patients lose weight and color, symptoms which are unfailingly noticed by relatives, especially parents. Children become languid with no desire to play, and adults are no longer able to carry on any heavy work. However, in the absence of complications they are never bedridden.

Epistaxes are present in nearly 75 per cent of the children. Bleeding gums seem more frequent in adults, although this order may be reversed. Nosebleeds may recur at frequent intervals and contribute not a little to the existing anemia. These and bleeding gums rarely exist simultaneously in one patient. Most adults, with or without kala azar, have severe gingivitis which no doubt contributes to the presence of this symptom.

Physical Signs

Before the recent influx of these patients during the last four years we almost unfailingly picked out the children with kala azar by their puerile countenances portraying an age much below the actual. Recently this has not been so for some unaccountable reason. Although the disease is called "black fever" in Chinese, the dusky appearance which is so common in India has not been present in our cases.

The striking features, in addition to those of a chronic illness, are the anemia and the emaciation of the trunk and extremities, the face remaining fairly full. We have failed to find edema of the feet and legs as a common sign. Neither have we noticed engorgement of the abdominal veins, although these two signs have been reported as usual findings by others. Their absence may be due to the short duration of the disease.

Little needs to be said regarding the general physical examination. There may be a systolic murmur which is probably an accompaniment of the anemia. Muir [43] mentions a low blood pressure, but on this point we are unable to make any observations as most of the patients were treated in the clinic where this was not measured.

Enlargement of the spleen has already been mentioned. It usually extends downward, although occasionally it may project to the right of the umbilicus before passing below it. It is usually fairly thick, but in young children it sometimes feels less than the thickness of a palm. In cases in which it has grown rapidly the spleen may be soft and almost pliable, whereas in older cases it is firmer. Its original contour is usually maintained. There were only six of the 585 cases whose spleens were not palpable. A study was made of the size of the spleen as related to the estimated length of disease, dating its onset at the first febrile period. In 58 per cent of those patients with a duration of illness under three months the spleen was above

the umbilicus as compared with 49 per cent of those with a six month illness. Therefore in patients with a disease of over six months' duration there was an even higher percentage reaching below the umbilicus, and a still further increase after 18 months. From these findings it may be inferred that the rate of enlargement is greatest during the first six to nine months of illness.

Muir [43] and others have stated that there is a characteristic rise of temperature twice a day. In a series of 49 uncomplicated in-patients there was only one who showed this curve. Most of the patients had a malarial type of fever with a daily rise and fall, and a smaller number maintained a continuous low grade fever until it fell with treatment. Children showed less fever than adults, even when their disease was of longer duration.

FIG. 2. A child with kala azar having situs transversus.

In this same group of in-patients undergoing treatment the elevation of temperature averaged less than 100.5° F. in 90 per cent of the cases. There were occasional peaks of fever far above the average, but these were unusual. A comparison of the pulse rate with the fever revealed a much more rapid pulse than would be expected for the temperature. This may be due to the cachectic condition of most in-patients, those less ill being treated in the clinic. Sixty-six per cent of the 49 uncomplicated in-patients undergoing treatment maintained a continuously normal temperature after the eleventh day, only four of these being afebrile at the outset. All groups of patients, regardless of age and duration of the disease, responded similarly to treatment, although those over 10 years of age with an illness under six months became free of fever sooner than others.

Laboratory Findings

Indirect Evidence

1. *Anemia.* This was frequently striking and usually seemed to be of the simple secondary type with no demonstrable variations from the normal erythrocyte morphology. However, on frequent occasions, especially in more advanced anemias, there was definite hypochromia. The erythrocyte count was reduced in proportion to the hemoglobin. Unfortunately insufficient records were obtained after treatment for comparison, yet there was no question but that the anemia began to improve soon after commencing treatment, even without supportive iron therapy.

Table II

Hemoglobin *

Hgb. %	10–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	76–80
No. cases	1	4	5	11	13	36	16	46	19	20	22	36	5	4
% cases	.42	1.70	2.1	4.62	5.46	15.1	6.75	19.3	8.0	8.4	9.24	15.1	2.1	1.7

* Estimations performed on a standardized Sahli instrument.

This table shows that 55 per cent of the patients had a hemoglobin reading of 50 per cent, or under. Studying the cases individually, there was a tendency for a greater degree of anemia in patients with a disease of longer duration, especially in children.

2. *Leukocyte counts* are reported in table 3, and will be discussed thereafter. An increase in the white cell count was one of the first signs of successful treatment, occurring even during treatment. Complete remission was secondary to an increase in the number of leukocytes, as illustrated by apparently spontaneous cures which follow a leukocytosis from complications, such as noma.

Table III

Leukocyte Counts

	1500	2000	2500	3000	3500	4000	4500	5000	5500	6000	over 6500
No. cases	24	28	45	37	22	31	24	19	8	8	33
% cases	8.6	10.13	16.12	13.25	7.87	11.1	8.5	6.9	2.87	2.87	11.79

This table shows that over 50 per cent of the patients had counts below 4,000 per cu. mm. Contrary to our expectations younger patients revealed a better leukocytic response, even with a long standing illness, than did the older patients, many of whom had been ill for less than six months. Patients over 10 years of age with a disease of over six months' duration quite definitely showed the poorest response, 55 per cent having counts below 3500

per cu. mm. This may account in part for the higher incidence of complications in older patients with a protracted illness.

3. *Differential counts.* Unfortunately these were not carried out routinely on uncomplicated cases, but there is no question as to the lowering of the polymorphonuclear percentage and an increase in lymphocytes.

4. *Platelet counts and bleeding times.* A series of these examinations carried out on two small groups, with and without epistaxis, failed to show any definite relationship of this symptom to thrombocytopenia or a prolonged bleeding time.

5. *Water test (globulin precipitation, or hemolytic test).* This is positive because of an increase in serum globulin which is also present in Banti's syndrome, schistosomiasis, chronic malaria and occasionally typhoid fever.[44] Positive reactions are graded from 1 to 4 plus, and in nearly all cases the reaction is strongly positive. This test remains positive for a number of months after remission following treatment.

In the presence of a positive water test together with leukopenia and splenomegaly, we consider the diagnosis certain and give treatment even if Leishman-Donovan bodies are not found in the marrow or liver smears.

Other indirect tests for kala azar are the formol-gel and antimony reactions which will not be discussed as we have not used them.

Direct Evidence, or Demonstration of the Leishman-Donovan Bodies

1. In the blood.

a. By smear. This was relied upon before liver and sternal punctures were used. It is possible, if not probable, that these would frequently be positive if smears could be made during the first febrile seizures when the parasites may be in the blood stream. Wang [45] found blood smears positive in 39 per cent of his cases. The smear was made so that it was thick at the end where leukocytes and parasites accumulated.

b. By blood culture. This method is described in Cecil's Medicine using blood diluted with N.N.N. medium. It is incubated 6 to 18 days at 22° C. to prevent the growth of other organisms, which even then is frequent. But it is usually positive, the flagellate form appearing.

2. In the lymph nodes parasites have been demonstrated either in a biopsy section, or in the material removed by a trochar.

3. In the spleen. Splenic taps have long been employed routinely and are usually positive. Muir [43] described this procedure, giving a careful account of his technic in 1,000 examinations without a mishap, employing carbolic acid as a skin anesthetic. However, owing to splenic friability and danger of hemorrhage, this method of diagnosis has been largely abandoned. We used it only twice in as many years in cases presenting unusual diagnostic difficulties.

4. In the liver. In spite of a similar danger of hemorrhage from tearing, especially in crying children, this method is still used routinely by many

examiners. Although only a very small amount of tissue is removed, a fine bore hypodermic needle being used, parasites are almost invariably present and easily found.

5. In the bone marrow. Aspiration of tibial marrow was first carried out, but because of the thickness of the cortex this site was impractical. Examination of the bone marrow for Leishman-Donovan bodies did not become popular until the introduction of sternal punctures. Our use of this method was initiated by an article by Chung [46] in 1938. We have employed the usual technic in making sternal punctures. A fine caliber spinal puncture needle which had been shortened to approximately one inch in length was used. A few drops of marrow were withdrawn by a small syringe. The marrow was spread on a clean slide and was stained by Wright's or Leishman's stain. A longer time is necessary than for blood cells, as the parasites absorb the stain more slowly. (This method has also proved valuable in the diagnosis of malaria in difficult cases.)

In case the sternal smears were negative, then leukocyte counts, hemoglobin determinations and water tests were done. If these were characteristic of kala azar and if the spleen was enlarged, there was ample indication for treatment. On the other hand, if these were all negative but if the spleen was enlarged, a liver tap was done. In case this also was negative, the patient was told to return in one month for a further examination. However such instances were rare. At times a second sternal puncture was carried out instead of a liver tap.

TABLE IV

Sternal Punctures and Liver Taps

Sternal Puncture	Positive	Negative	Total	Liver Tap	Positive	Negative	Total
First	452(81%)	105(19%)	557	Original	2		2
Second	3(38%)	5(62%)	8	After sternal puncture	24(53%)	21(47%)	45

6. Leishman-Donovan bodies are also found in the tonsil and nasal smears,[22] and also in the feces. Owing to the difficulty of finding them, these examinations are of only experimental interest.

DIFFERENTIAL DIAGNOSIS

When the parasites are found there is no question as to the diagnosis. When they are not identified and other supportive findings are absent, which is infrequent, the question of diagnosis arises. Chronic malaria, Banti's syndrome and schistosomiasis (prevalent in the Yangtze valley) should be considered. More acute infections, such as malaria, typhoid fever, Malta and relapsing fevers, may also be simulated by kala azar.

Complications

When a remission followed treatment the patient rarely had any subsequent illness. Therefore other diseases were coincident with the kala azar itself. Complications were relatively more common in adults than in children. Most patients with complications had a resistance lowered by a protracted disease, and also had an especially low leukocyte count with which to combat the invading organisms. When children were attacked, they seemed better fitted to resist the added disease, even when quite ill from the kala azar. Naturally most complications occurred in children as their number was so much greater.

The following table includes the most frequent complications and causes of death observed in the 585 patients. As many patients had more than one complication, there was a greater number of these than the number of patients thus affected. Practically all new patients who were severely ill were admitted to the hospital. Out of the entire group there were 30 known deaths, a mortality rate of 5.1 per cent. Four of these were in clinic patients, three of whom had no complications.

Table V

Complications

Diseases	Surviving		Deaths
	Clinic	Admissions	
Pneumonia (all forms)	3	12	9
Acute bronchitis	15	5	
Acute pharyngitis	5	1	1
Gangrenous stomatitis (noma)	5	7	3
Fusospirochetosis		2	3
Bacillary dysentery	15	5	1
Amebic dysentery		1	
Diarrhea (undetermined cause)	12	2	
Ascites	3	7	
Acute (glom.) nephritis		6	1
Edema	4		
Otitis media	4	1	
Abscess (post injection)	4	2	

Other complications were lung abscess, acute pleurisy, pulmonary tuberculosis, empyema, acute laryngitis, diphtheria, bacterial endocarditis, poliomyelitis, gonorrheal conjunctivitis, acute cervical adenitis, synovitis, parotitis, chickenpox, idiopathic purpura, streptococcic and staphylococcic bacteremia and erysipelas. Deaths also occurred with pulmonary tuberculosis, empyema, pleural effusion, Ludwig's angina, bacterial endocarditis, intestinal hemorrhage from typhoid fever and advanced anemia.

Special mention should be made regarding the complication of noma. This dreaded condition has been the cause of death in many patients, whereas in others it has apparently resulted in a remission (cure). In our series it

occurred only in one patient over the age of 15, which corresponds with the observations of others. Infrequently older men are seen with noma scars and state that when young they had enlarged spleens which disappeared without treatment after the noma had healed. Clow [19] mentioned the frequency of bronchitis and dysentery in 100 cases, 14 of whom had noma with a death rate of 64 per cent. Fan and Scott [17] reported a 15 per cent mortality rate in 20 cases of kala azar with noma. Two of our three deaths in patients with noma occurred shortly after admission before treatment was started, and seemed to be due to a severe toxemia from the infection. In the third patient treatment had been completed and there was a rise in hemoglobin and leukocyte count before the patient succumbed to heart failure following bacterial endocarditis.

Relapses and Immunity

Although each patient was told to return a month after treatment was concluded for an examination and sternal puncture, so few followed this advice that it does not seem worthwhile to make a detailed report of these cases. It is probably safe to say, however, that those patients who successfully completed treatment without any mishaps returned home to regain good health. Those who did return for reëxaminations frequently still showed Leishman-Donovan bodies in their marrow. If the general condition was good, this finding was disregarded for the time and the patient was told to return in another month for a second smear. In such cases this was usually negative. (It has already been mentioned that the parasites disappear from the marrow more slowly than from the spleen and liver.) Therefore, although for diagnosis the finding of the parasites was of supreme importance and the other blood changes and symptoms were secondary, in determining relapses it was more important to check the leukocyte count, hemoglobin and general condition. Provided these were favorable, the continued presence of parasites did not indicate that the disease had not been treated satisfactorily. On the other hand, in cases which presented a continued leukopenia, cachexia and anemia after treatment, even if parasites were not found, a second course of treatment was seriously considered.

In this series there occurred six known relapses. Three of these appeared several months after treatment, and would therefore seem to be due to insufficient dosage. The other three had an apparently normal health period ranging from 6 to 24 months, during which time there was not only a remission of clinical symptoms, but also an absence of parasites in the marrow and liver smears. We may consider that such cases, in spite of a long remission period, are also probably relapses due to insufficient treatment, although there is some possibility of a reinfection.

Immunity. The work on this problem is still largely in an experimental stage and is bound up with the apparent equivalence of *L. canis* and *L. donovani*. Chung and Wang [32] cured five hamsters of *L. donovani* infection,

after which two of these were relatively and three completely immune to reinfection with *L. canis,* the controls having died. Chung [39] in cross complement fixation examinations found that antigens of *L. donovani* and *L. canis* gave equally strong positive complement fixations, supporting the theory that the two forms of leishmania are identical. Wang and Chung [47] treated 13 hamsters having kala azar with 20 grams of neostibosan per kilogram. (This is 400 times the dose used for man, which is about 50 mg. per kilo.) In this series they obtained only a 47 per cent cure after six months. Out of these, six became partially immune to a second infection, and four completely so. The excretion of antimony may be faster in hamsters than in man, and this may account for the need of larger doses, and a lower rate of cure.

Prophylaxis

This is based on what is known of the epidemiology of the disease and would consist of the eradication of dogs with leishmaniasis, the removal of such conditions as would contribute to the breeding of sandflies, and the isolation of cases.

Course and Prognosis

In China the course of the disease is long. After a variable period of normal activities the patients become weak, emaciated and anemic so that they are unable to work or play. Fever accentuates their anorexia and augments these symptoms. However, they remain ambulant until some complication supervenes and death ensues. Only three of our cases died of uncomplicated kala azar. Under treatment, if there are no complications, a remission follows in an almost unbelievably short time considering the length of illness in most patients. When treatment was first started, in some patients there was found an actual enlargement of the spleen or tenderness on palpation. It is an interesting question whether or not this is associated with the stage of proliferation described by Wang [42] in hamsters undergoing treatment. In approximately one-third of the patients there occurred a rise of temperature after the first or second injection. This was brief and may have been due to the drug. After the fall in temperature there followed an increase in leukocytes and hemoglobin. Clow [19] reported an average increase of 2,510 leukocytes and 4.5 per cent hemoglobin during treatment in 100 cases. After discharge the patients regained strength and weight, the spleens gradually became smaller and within a few months children were once more able to play and adults return to their occupations.

Treatment

It has been only a few decades since multivalent antimony compounds became available. Thereupon kala azar could be adequately treated with a rate of cure of 90 per cent or more, and with little fear of drug reactions. Prior to this, treatment was risky and unsatisfactory.

To produce leukocytosis. With the discovery of leukopenia it was believed that a remission would follow an increase in the white cell count. In order to accomplish this a number of methods have been employed. In Syria a seton was introduced through the skin over the spleen by which means a permanent sinus was kept draining.[43] In China a large number of patients come in with a plaster of local medicine applied over the enlarged spleen. Whether or not there is any effect on the leukocytes cannot be stated.

Physicians have also tried to produce leukocytosis by injections of sodium nucleate, staphylococcus vaccine, or by camphor, creosote and turpentine in olive oil. Hu [48] studied the influence of parenteral injections of dead bacteria and foreign proteins on experimental kala azar infection in hamsters. His experiments showed a larger spleen in these hamsters than in a series of untreated controls, because of a reticulo-endothelial proliferation and cell infiltration, but with fewer parasites.

To eradicate the parasites. Tartar emetic was probably the first antimony compound used in the treatment of kala azar. It was given in a 1 or 2 per cent solution intravenously, starting with doses of 0.5 increased to 3 c.c. Three injections were given weekly over a period of nearly four months, until a total dosage of 2 to 4 gm. had been administered. Many reactions and complications occurred, especially broncho-pneumonia. Similar doses of the heavy salt of sodium antimonyl tartrate were used by Muir.[43] This drug was less toxic, and produced remission of fever in a month.

Urea stibamine has been used chiefly in India, with no ill effects, but it seems that little of the compound has been available in China, although one observer [49] gave a short report on its effect. He stated that it was more potent and more toxic than neostibosan, and was not so well standardized as the antimony content varied from 20 to 43 per cent.

Neostam is a pentavalent antimony compound which was used extensively in many if not in most of the largest kala azar clinics in China. Its dose is based on body weight, being approximately one gram for each 33 pounds. Although many who used it reported that reactions were unusual, we did not find its use in the clinic feasible because of severe vomiting and at times diarrhea. Clow [19] also mentioned vomiting as a distressing reaction. Bed patients rarely react to it, but as most of our patients were treated in the clinic we gave it to a smaller portion of the entire series. There were several hundred of these, and they responded as satisfactorily as did the others who received neostibosan. However, many of this group suffered an accentuation of their bronchitis under neostam, which rarely occurred with neostibosan.

Neostibosan (diethylamine p-aminophenyl stibinate) containing 42 per cent antimony was the drug which we used most regularly as reactions were mild or absent and as it was uniformly effective. The dose was similar to that of neostam, although with children under 33 pounds a full gram was given, and three grams cured adults weighing up to 110 pounds. Usually the largest dose employed was 3.5 grams, although for a period we occasionally gave as much as 4 grams. This was still a smaller dose than some others have used, but our results would seem to justify it.

Clinic patients received three injections a week on alternate days with individual injections varying from one-fifteenth of the total dose at the out-

set, to one-eighth toward the last of the course. Children usually finished the treatment in nine injections, and adults in eleven. In-patients received daily injections as they could be kept in bed and their condition observed more accurately. These completed their treatment in 13 to 16 days as somewhat smaller doses were given daily than when administered every other day.

The dangers of a routine system of dosage based on weight are many, as individual variations require readjustments in many instances. We tried to accommodate the dose to such variations, but no doubt sometimes failed. Occasionally a larger amount of antimony is needed, especially in those who are more severely ill, but not necessarily in those with a longer history. Practically all injections were given intravenously in 0.5 per cent solution because when the drug is given intramuscularly sterile abscesses may occur.

Antimony is definitely contraindicated in the presence of jaundice, hepatitis, nephritis, or pneumonia. Although in the presence of bronchitis treatment was given, the patient was admitted as pneumonia might ensue. If we had withheld treatment in all cases of bronchitis, many would have been left untreated. We also gave the drug in the presence of ascites without any untoward reactions.

Whether or not it is advisable to withhold treatment in the presence of noma seems to be an undecided question. Some authorities advise this, and await the limitation of the process. Chu [49] and Fan and Scott [17] continued routine treatment not only without misadventure, but even with good results. This is the procedure we followed, and neither did we meet with any adverse reactions, but rather found that these patients responded well with an early limitation of the necrotic process.

In conclusion it must be admitted that so little is known of the antimony concentrations necessary to be parasiticidal, of its storage in the body and of its elimination rate that treatment is based on purely empirical grounds. It is hoped that in the future there will be introduced suitable analytical methods which will answer these questions.

Conclusions

1. Kala azar is endemic throughout north China with an especially high incidence from southern Shantung to the Yangtze River. The disease seems to follow in the wake of famine, flood, drought and war.

2. It is most common below the age of 15, although this series contained an unusually large number of patients from 15 to 40 years of age. Most of the patients are from the farmer or coolie class living in small villages.

3. A study of the epidemiology points to the sandfly as vector, and the dog as reservoir host for the parasites. This is borne out by (*a*) the ability of *Phlebotomus chinensis* to receive and retain the parasites even in the absence of blood, (*b*) the growth of flagellates in the intestine of the fly and their forward extension into the proboscis, (*c*) the apparent identical nature of *Leishmania canis* and *donovani* as revealed by similar complement fixation

reactions, and (*d*) direct transmission of the disease to man through the bite of infected flies.

4. The most important physical signs are an enlarged spleen usually reaching to the umbilicus within 12 months, a low grade fever with tachycardia, an anemia most pronounced in children with a longer illness, and a leukopenia which is more marked in the older and more chronic cases. All uncomplicated cases remained ambulatory.

5. Sternal marrow smears were positive in 81 per cent of 557 examinations, and constituted the most valuable means of diagnosis.

6. Complications were more frequent in older patients with a more protracted history. The most common of these were pneumonia, amebic and bacillary dysentery, bronchitis and noma.

7. There were 30 known deaths in 585 patients, a mortality rate of 5.1 per cent. Only three of these succumbed to kala azar alone, the remaining having complications, the most frequent of which was pneumonia.

8. Six relapses were known to have occurred, three within a few months and three after a period of normal health and negative laboratory findings extending from 6 to 24 months.

9. Prophylaxis should consist of eradication of sandfly breeding places, removal of infected dogs and segregation of patients.

10. The course of the disease is chronic. Untreated cases gradually lose weight and strength until their debilitated condition makes them subject to some complication which is usually the cause of death. Kala azar responds readily to antimony treatment even in patients with a chronic infection.

11. Our treatment has consisted in the use of pentavalent antimony compounds (neostibosan and neostam), giving approximately one gram per 33 pounds of body weight in 9 to 16 intravenous injections of a 0.5 per cent solution. Very few reactions occurred with neostibosan except a brief fever at the outset of treatment. Gastrointestinal upsets were common in clinic patients receiving neostam, although these were rare in in-patients. After treatment the parasites disappear more slowly from the bone marrow than from the liver and spleen. Antimony is contraindicated in the presence of jaundice, hepatitis, pneumonia, or acute nephritis.

12. Before a sound rationale of treatment can be laid down, more information must be obtained concerning the least concentration of the drug which is parasiticidal, its storage in the tissues and rate of elimination.

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PERIARTERITIS NODOSA: OUR PRESENT KNOWLEDGE OF THE DISEASE*

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IN these days of chaos it may be stimulating to turn from subjects relating to war to a topic which dates from 1866, when Kussmaul and Maier [1] observed their first patient with arteritis. In their classical protocol a description of periarteritis nodosa is given in a patient who had enteritis, nephritis, and neuritis. In 1939 Harris, Lynch, and O'Hare [2] reviewed a total of 101 cases of periarteritis nodosa which had been reported in the English literature up to that date. From 1939 to 1942 we observed a group of seven male patients who came to autopsy with necrotizing lesions of the arteries and veins involving many organs, and this interest was further stimulated by our observation of five male patients who came to postmortem examination in a period of two months at Walter Reed General Hospital.† Since the beginning of the present war more than a score of soldiers have come to autopsy with this disease entity, the diagnosis being frequently made before death.‡ This fact emphasized our belief that the disease is not the rarity that it was once thought to be.

ETIOLOGY

The etiology of this disease is unknown. Syphilis was long thought to be a causative factor, but this belief has not been borne out. This contention was largely based upon the observations of Chvostek and Weichselbaum,[3] whose patient had pupillary changes associated with encephalitis. In 1925 Gruber [4] reported his group, two of whom had positive serologic reactions. So far as we are able to determine from the literature, no observer has demonstrated a spirochete in a patient with necrotizing arteritis. It seems unlikely that syphilis plays any rôle whatsoever. A few clinicians have associated allergic manifestations with this disease. Harris and his associates have found allergy associated with 15 per cent of their patients. Rackemann and Greene [5] made a report at the Association of American Physicians, in 1939, relating the close association of asthma with periarteritis nodosa. Von Haun [6] and Harris [7] have been able to produce similar lesions in the arteries of rabbits by injecting the animals with bacterial products. There were

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many points of similarity in our group suggesting a common infectious or toxic origin. The wide dissemination of the lesions, affecting the branches of the middle and small caliber vessels of almost every organ, has influenced us in our belief that they have a toxic etiology. The toxic origin of this morbid process has been thoroughly discussed by us.[8]

Clinical Manifestations

The clinical symptoms of our group were protean, because so many organs were involved. The onset was insidious, and often appeared subsequent to some obscure infection. The chief symptoms have been malaise, anorexia, asthenia, myalgia, and weight loss (figure 1). There was moderate weakness and cachexia. The temperature curve was either septic with

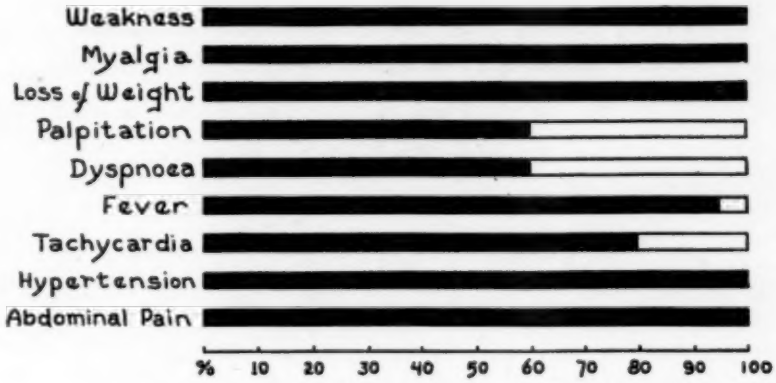

Fig. 1. Signs and symptoms of periarteritis nodosa (our series).

chills or was of the low, irregular variety. Complaints referable to the gastrointestinal tract were frequently encountered, but loss of appetite and vague abdominal distress were the most common problems. Ulceration of the mouth and diarrhea were less frequently noted. Evidence of cardiac involvement included precordial distress, palpitation, tachycardia, and congestive failure. Pericardial friction rub appeared late in the course of the disease on two occasions. The peripheral vessels were sclerosed far beyond the numerical age of the patient. There were signs of acute or chronic nephritis, with hyaline and granular casts, albuminuria and hypertension. Peripheral neuritis and paresthesias were sometimes seen early in the course of the disease. Obviously, all of the symptoms and signs cannot be enumerated, since necrotizing arteritis may mimic, at the same time, one or several diseases depending upon the organs affected (figure 2). For this reason we have scrutinized arterial changes in every young male with particular care. Pulsating subcutaneous nodules, thickened peripheral arteries, diminished or absent pulsation in a peripheral artery, gangrene, and Raynaud's phenomenon, associated with arterial obstruction, were suggestive and

helpful signs. The clinical picture in our patients varied strikingly, depending on the distribution and severity of the vascular lesions. In male patients with obscure, bizarre, and contrasting symptoms suggesting cachectic or infectious disease, the possibility of necrotizing arteritis was always considered.

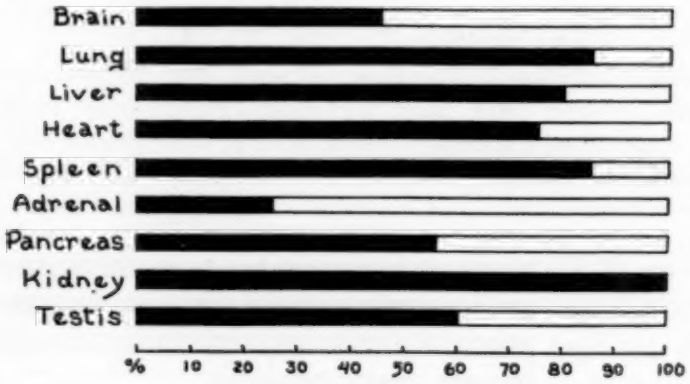

FIG. 2. Organs involved in periarteritis nodosa (our series).

PATHOLOGICAL MANIFESTATIONS

1. Pulmonary manifestations. Ophuls [9] demonstrated extensive involvement of the pulmonary arteries and infiltration of the pulmonary parenchyma in his patients. In Gruber's series, four patients showed thromboses in the pulmonary vessels. In 1933 Herrmann [10] reported certain pulmonary changes in the roentgenogram of a patient with periarteritis. However, Herrmann's patient had suffered with severe asthma, whereas none of our patients had a history of any such allergic state. Our first patient had normal chest films until late in the course of the disease, when small conglomerate areas of increased density were noted at the bases, accompanied by diffuse infiltration, spreading out irregularly from the hilar zones (figure 3). As all of our later patients have died with bronchopneumonia, the roentgenograms taken before death revealed hilar and basal shadows of increased density, sometimes associated with areas suggesting cavitation and accompanied by a variable amount of pleural reaction. Pleural effusion was encountered in five instances, and empyema occurred just before death in a 32-year old soldier. Atelectasis was found bilaterally in several patients, but it was thought to be a terminal event associated with the pneumonic process. Large pleural effusions and empyema were rarely seen, but both bronchopneumonia and small effusions were regularly demonstrated. We believe that the pulmonary changes are frequently more extensive than roentgenograms and clinical observations disclose, and this was corroborated frequently at postmortem examination.

2. Gastrointestinal manifestations. All of our patients complained of vague abdominal distress, frequently associated with anorexia, but rarely

with vomiting. Terminally one soldier had two days of pernicious vomiting associated with right upper quadrant rigidity and tenderness. At autopsy the appendix showed early gangrene due to thrombosis of the appendiceal artery. Small petechial hemorrhages were occasionally found in the stomach and small bowel mucosa, and frequently there were arterial changes in the celiac and mesenteric vessels. The right superior gastric artery was completely thrombosed in one patient who was only 26 years of age. Chronic pancreatitis was noted in 50 per cent, as shown by increased fibrosis and small

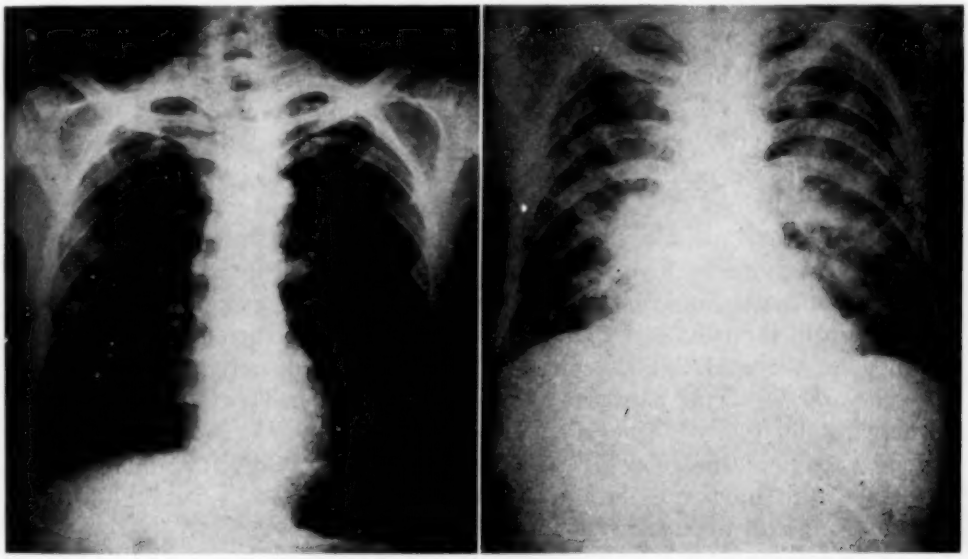

FIG. 3. (A) Chest film taken six weeks before death shows no cardiac enlargement. A slight increase in the hilar shadows is noted. (B) Chest film taken of the same patient, one week prior to death, reveals slight enlargement of the heart shadow. There is a marked mottled density throughout both lungs, which is prominent at the lung root and extends well out into the periphery. These changes are often associated with extreme congestion of the pulmonary vessels.

areas of fibrinoid necrosis, which may account for the frequency of abdominal distress, even though diarrhea was encountered rarely. Several pancreatic specimens showed numerous vessels obliterated by thrombi. Three of the patients included in Gruber's study showed infarction with hemorrhage into the pancreas. Lamb [11] also mentioned infarction of the pancreas in his group.

3. Hepatic manifestations. Upper abdominal cramps were complained of frequently, but it was impossible to determine whether this was due to hepatic involvement. Clinical jaundice was present in three instances. Klotz [12] observed two patients with jaundice, whose histological examination showed areas of hepatic necrosis with hemorrhage, and thrombosis of the hepatic artery. In one of his patients liver necrosis was associated with

thrombosis of the cholecystic artery, and portal fibrosis similar to that seen in cirrhosis of the liver. Kountz [13] observed a patient showing icterus and peripheral neuritis, whose cholecystic artery and vein revealed thromboses. Pass [14] reported that periarteritis was the most frequent cause of infarction of the liver. Our specimens showed lesions in the hepatic vessels, but there was insufficient damage to produce cirrhosis.

4. Endocrine manifestations. Weakness was a complaint common to all, and it was profound in four patients. Whether this complaint had any direct relation to the adrenal changes cannot be said. However, the small adrenal arteries were occasionally surrounded by thick cuffs of monocytes, polymorphonuclear cells and plasma cells. Phlebitis and periphlebitis were sometimes noted, and, occasionally, complete occlusion of a vessel was found. Involvement of the testicular arteries and veins was noted in our first patient. We have found fibrinoid necrosis of the vessels four times. Just what disturbance occurred in the reproductive physiology was not determined. No lesions of the thyroid or pituitary vessels were found.

5. Neurological manifestations. Peripheral neuritis, associated with gangrene, was noted in two patients. Uncomplicated neuritis was evident in four others. Some complained of weakness and extreme fatigability, with pain in the calves of the legs after exercise. Occasionally, tenderness along the peroneal nerves could be elicited without any reflex changes. Twenty of Gruber's patients were said to have had peripheral neuritis, whereas only two of Spiegel's [15] group had peripheral involvement. The blood vessels of the cortex were occasionally infiltrated with inflammatory exudate with moderate thickening of their walls. Gross cerebral hemorrhage was never observed.

6. Renal manifestations. Moderate hypertension was a constant feature, being noted in every patient in this series. Moreover, albuminuria, with hyaline or granular casts, was common to all. Nitrogen retention was present terminally in 60 per cent, but the degree of nitrogen retention was not sufficient to produce uremia. Urea clearance was diminished in those patients showing nitrogen retention. That renal involvement is common in arteritis was noted by Arkin.[16] All of Spiegel's patients, who came to autopsy, had renal lesions. The lesions of malignant nephrosclerosis and those of chronic glomerulonephritis were occasionally encountered. These findings would suggest the vascular reaction in these kindred diseases might be caused by a similar toxin, or infectious agent.

7. Cardiac manifestations. Precordial distress and palpitation were frequent complaints. Heart consciousness and dyspnea were relatively common. The heart was enlarged terminally in all patients. In one patient the cardiac shadow widened just a few days before death. Sections taken through the endocardium have revealed inflammatory changes in three instances. No Aschoff bodies were found, but the valvular lesions appeared similar to those seen in acute rheumatism. This is in agreement with Fried-

berg and Gross,[17] who recorded four patients with the clinical picture of rheumatic fever, showing the valvular and myocardial lesions generally regarded as characteristic of rheumatic heart disease as well as valvular lesions characteristic of periarteritis nodosa. They believed that the arteritis in their group of patients was an expression of the rheumatic state. Both diseases probably have a common etiological factor, so it is conceivable that

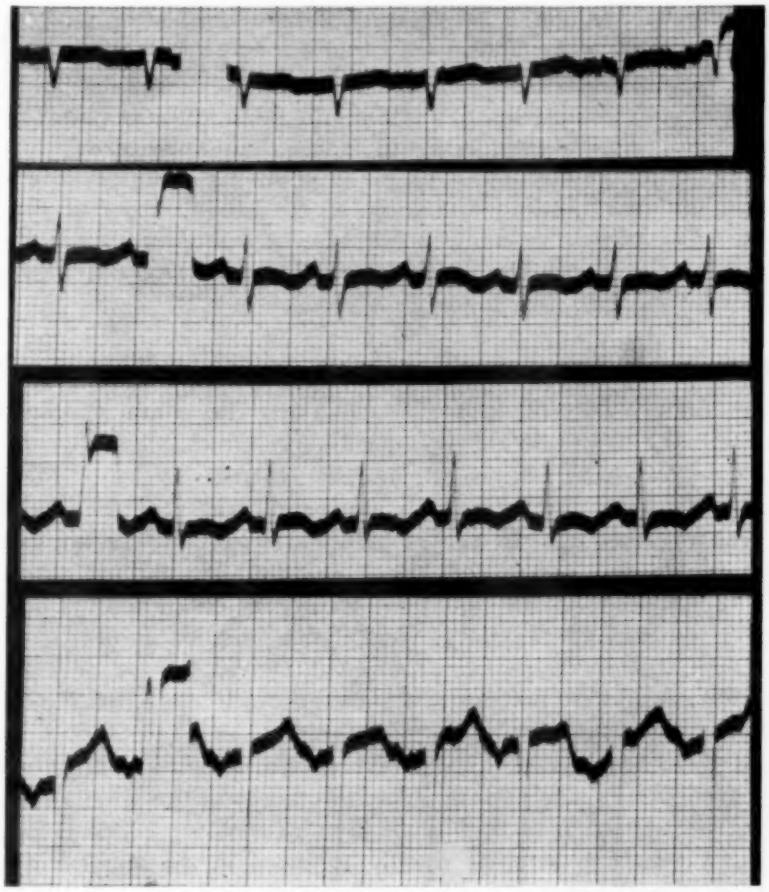

FIG. 4. Right axis deviation is indicative of increased pressure in the pulmonary circuit. T-wave changes indicate myocardial change.

these rheumatic lesions were due to necrotizing arteritis. It is a well known fact that verrucose vegetations are not specific of rheumatic carditis. Even Aschoff bodies may not be specific of the rheumatic state. Pericarditis was found on four occasions, and in one instance it was associated with dilatation of the ascending arch of the aorta. Branches of the coronary artery and vein were thrombosed in two of our group. Abnormal electrocardiograms were noted in the last weeks before death in all of our group (figure 4).

8. Cutaneous manifestations. Various skin lesions were found in 20 per cent of these patients. Among these were neurodermatitis, simple erythema, subcutaneous nodes and necrotic lesions.

9. Joint manifestations. Joint pain or myalgia was common to all. Actual joint swelling was observed in two soldiers, but there was no evidence of redness. Painful nodules were biopsied whenever they were found. These biopsies were never pathognomonic, but they revealed evidence of an inflammatory reaction about the small vessels.

10. Laboratory manifestations. From a laboratory standpoint the data obtained were those frequently noted in many chronic diseases. It was usual to find a moderate leukocytosis, but we have seen the leukocyte count elevated to 45,000. Eosinophilia was found in three patients, the highest being 7 per cent. Abnormal urinary excretion was common to all, manifested by albuminuria, cylindruria, and abnormal cellular content. Nitrogen retention was evident terminally in 60 per cent. *Staphylococcus albus* bacteremia was demonstrated in one soldier who had developed empyema due to the same organism.

Discussion

Many early observers stressed the periarteritic characteristics of this morbid process. It has been shown that the periarteritic lesions, occasionally striking on gross examination, are not the essential lesions of the malady. We have found that involvement of any or all grades of the blood vessels themselves might occur. In fact, not only arteries, but also the veins were involved (figure 5). From this standpoint the term periarteritis has been entirely too limited insofar as nomenclature is concerned. The disease, from a strictly anatomical point of view, may be divided into the macroscopic form which is recognizable from the obvious gross lesions, and the microscopic form which may be suspected indirectly by the multiplicity of lesions referable to the blood vessels.

Until recently many of the less evident pathological changes were not observed on gross examination, and unless serial sections have been made, the area of necrosis may well have been overlooked. The characteristic lesions of necrotizing arteritis usually appeared in the small and medium blood vessels, affecting as a rule the inner portion of the media and the intima. With the involvement of the intima one expected subendothelial proliferation, and with involvement of the media, elastica disruption and necrosis of the muscle occurred. The necrosis has been of a peculiar fibrinoid nature closely resembling that which has been observed in various manifestations of Libman-Sacks disease, malignant nephrosclerosis, and rheumatic fever. The kaleidoscopic manifestations of these diseases and the multiplicity of their lesions have been confusing. In patients with malignant nephrosclerosis one could very readily overlook the concomitant manifestations of the malady discussed in this paper. In patients with active rheu-

matic fever the presence of symptoms suggestive of glomerulonephritis has suggested to us a possible combination of necrotizing arteritis and rheumatic fever. In dermatomyositis one must differentiate this disease as an entity from dermatomyositis occurring in combination with periarteritis nodosa, and from dermatomyositis as it occurs in Libman-Sacks disease. A muscle biopsy without complete clinical data was not adequate in our ex-

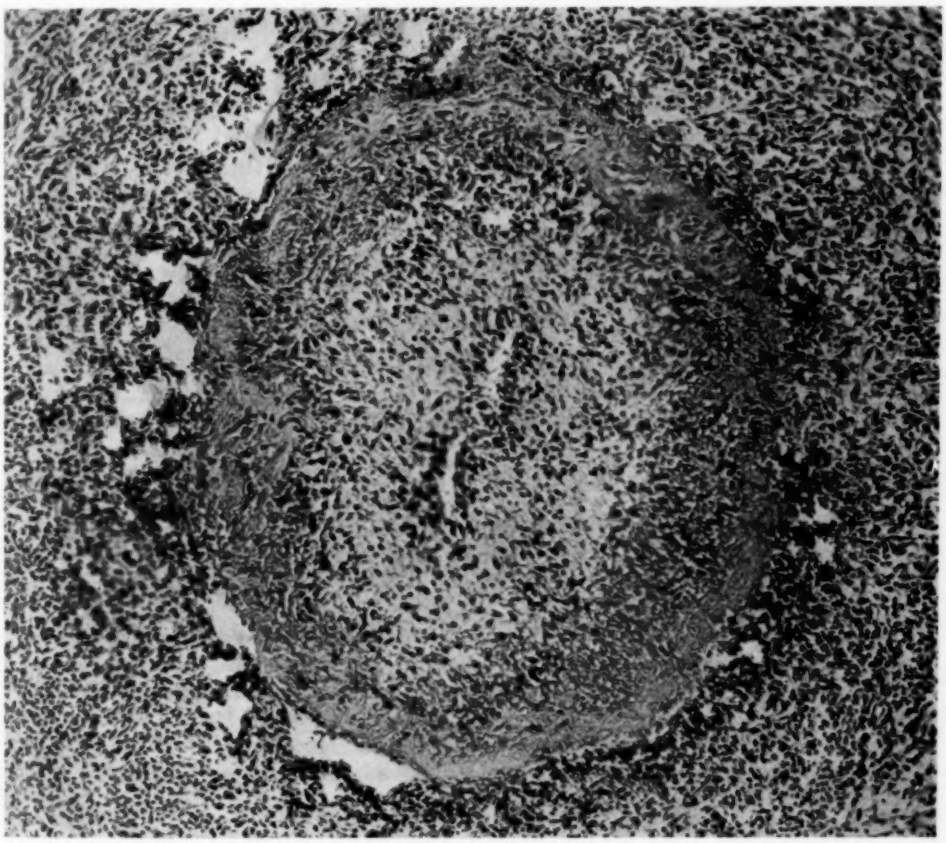

FIG. 5. Histological section of periadrenal vein showing diffuse phlebitis and periphlebitis with partial occlusion of the lumen. (Giemsa stain × 400.)

perience to enable us to differentiate these various forms of muscle disease. Arteritis apparently occurs in an acute or accelerated form with a rapidly fatal outcome. According to Grant,[18] there is a more prolonged form in which the tempo of the disease is not only more tardy, but may be arrested and go on to the healing stage. In the accelerated variety, aneurysm formation and acute vascular lesions are found widely disseminated, and a fatality may follow the rupture of one of the former.

Prognosis and Treatment

There has been no specific treatment for this disease. All of our patients died. Sulfonamide therapy was used in seven patients without any apparent improvement. Papaverine hydrochloride was useful as a vasodilator for the relief of peripheral arterial spasm. Other opiates were used in combination with salicylate therapy for the relief of pain. Despite our unhappy experience, an occasional patient may survive.

Summary

We have reported the clinical manifestations of periarteritis nodosa in a group of patients coming to autopsy. The disease should be considered a pathological entity. Fibrinoid necrosis of the media of the arteries and veins was observed, similar to the changes noted by Von Glahn and Pappenheimer [19] in the peripheral blood vessels in rheumatism, and by Klemperer, Pollack and Baehr [20] in disseminated lupus erythematosus.

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PERIARTERITIS NODOSA, WITH REPORT OF THREE CASES DIAGNOSED DURING LIFE*

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PERIARTERITIS nodosa is a disseminated but focal inflammatory disease of the smaller arteries, of unknown origin. It is almost invariably fatal. The true incidence of the disease is unknown since there can be no proof of the diagnosis except by histologic examination of tissues obtained by biopsy or at autopsy. It occurs with equal frequency in both sexes and is seen in all ages. The literature contains reports of approximately 300 cases, the great majority of which have been diagnosed post mortem. The increasing number of reports dealing with the subject in recent years indicates better recognition of the disease rather than an increased incidence. This report concerns three cases which were diagnosed during life and confirmed by biopsy, autopsy or both.

Etiology. The disease is inflammatory in nature but its etiology is unknown. It is certain that no one microörganism or toxin is exclusively responsible. It seems more likely that any one of a number of different agents may initiate or lead directly or indirectly to the disease. Rheumatic fever has been suggested by some authors [1, 2, 3] as the cause although the weight of evidence is against this. A more plausible explanation has been offered by Rich.[4] He described vascular lesions characteristic of periarteritis nodosa in five patients who, shortly before death, had hypersensitive reactions following therapeutic injections of foreign serum, and in one patient who had received prophylactic sulfathiazole treatment against aspiration pneumonia. Clark and Kaplan [5] reported two cases with similar vascular lesions following serum therapy. Other authors [6] have noted the association of the condition with asthma. The frequent occurrence of eosinophiles in the peripheral blood and in the specific lesions is further supportive evidence. Thus it would seem that the disease is an anaphylactic manifestation, the arterioles being the "shock organ." It is unnecessary then to look for a single direct explanation for all cases since many bacteria, drugs or toxins can act as the sensitizing agents leading to this disease.

Clinical Picture. The clinical picture of the condition is extremely varied, and symptoms referable to many systems of the body are found. A brief consideration of the pathologic anatomy of this condition is essential for a proper understanding of the clinical disease. The term periarteritis nodosa is misleading since not merely the adventitia but all the coats of the

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vessels are involved and node formations are by no means an essential part of the disease. The fundamental pathologic change is an inflammatory lesion involving the medium and smaller arteries. Inflammatory cells, chiefly polymorphonuclear leukocytes, eosinophiles and lymphocytes invade the adventitia and soon involve the media.

The four stages of the process are described as the degenerative, acute inflammatory, granulating and healing phases respectively. Different stages of the process may be seen simultaneously in an individual case. As a result of the arteritis, there may occur necrosis of the wall with hemorrhage, aneurysms or node formations, thrombosis with infarction and (as part of the healing phase) recanalization.

The clinical and laboratory findings separate themselves into four large groups. First there are those occurring from the inflammatory process, such as fever, leukocytosis, general malaise, loss of weight, rapid sedimentation rate, anemia, and in general the picture of fever or sepsis of unknown origin.

Secondly one sees the symptoms which arise from the involvement of the arteries of particular organs, such as the heart (evidences of coronary artery disease, myocardial infarctions, heart failure), nervous system (peripheral neuropathy, visual disturbances, headaches), gastrointestinal system (abdominal cramps, vomiting, anorexia, bleeding, diarrhea), or kidneys (albuminuria, hematuria, azotemia, hypertension). It is thus seen that any system and in fact all systems may be involved leading to almost any combination of symptoms that the imagination can conceive. It is this irregular and baffling symptomatology which has resulted in such confusion and misdiagnosis during life. But if one gives the matter careful consideration the very protean nature of this symptom complex should lead one to consider this condition in the differential diagnosis of fevers of unknown origin.

The eosinophilia in the peripheral blood (in 15 to 20 per cent of the cases) and in the histologic sections of the involved arteries comes under a separate category probably representing an allergic manifestation. Two of our three cases had eosinophilia which was not marked—6 per cent and 7 per cent respectively. The incidence of eosinophilia will vary with the frequency with which differential white cell counts are done.

Palpable nodules along the course of subcutaneous vessels are helpful diagnostically when present, but they are not common. Two of our three cases had such nodules. Finally, in suspicious cases, a biopsy of a muscle should be done and careful histologic examination made of vessels in the removed tissue. The clinician should accept with caution a negative report since, as was noted in one of our cases, three separate biopsies failed to show any significant changes, although at autopsy there was no doubt about the diagnosis. Findings such as these serve to emphasize the focal nature of the disease.

Specialists in different branches of medicine have reported the disease

as simulating well known clinical entities. Allen [7] reported an instance which simulated an acute abdominal inflammation so closely that operation was performed before the diagnosis was made. Wechsler and Bender [8] have written an excellent report on the neurological manifestations of periarteritis nodosa emphasizing the predominance of peripheral nerve lesions. One author [9] has even described a sigmoidoscopic diagnosis of the disease. For more complete descriptions of the clinical findings, the reader is referred to articles by Baker,[10] Jones,[11] and Appelbaum and Kalkstein.[12]

Treatment. There is no known therapy for the disease. Goldman, Dickens and Schenken [13] reported the apparent cure of a case with sulfapyridine. This must be viewed with some skepticism in view of the fact that occasional instances of spontaneous recovery have been reported.[14] Indeed, the finding of healed (recanalized) arteritis in routine autopsy studies is not a very rare occurrence. Since no specific therapy can be suggested, the treatment must be supportive and symptomatic. In view of the theory that allergy is the background of this disease, a careful search for an allergen in individual instances would seem to be in order. However it is questionable whether removal of the allergen or desensitization would serve any therapeutic purpose. In one of our cases there was a positive finding of lead poisoning and in another instance the illness was preceded by an upper respiratory infection. In all three of our cases, by the time the disease was diagnosed, it was too far advanced to give any form of therapy a reasonable chance for success.

The following are the clinical protocols and brief autopsy findings of the three cases seen.

Case Reports

Case 1. A. D., a white soldier, aged 38, became ill during the first week of May 1942, with pain in the back of the legs and arms, for approximately five days following exposure to rain and cold. There was also a history of loss of weight. The past history was irrelevant except for the fact that he had formerly worked as a painter.

He was admitted to Fort Dix Station Hospital on May 12, 1942, appearing pale, asthenic, and poorly nourished. Temperature was 99.6° F., and pulse rate 110. The upper respiratory tract and mouth were normal. The lungs were clear both on physical and roentgenographic examinations. The heart rhythm was regular and no murmurs were heard. The blood pressure was normal. Abdominal examination including rectal was negative. He had pain and tenderness in the calves, thighs and biceps with no objective findings. The blood cell count showed 4,250,000 red cells with 80 per cent hemoglobin; the white cell count was 7,800 with 59 per cent polymorphonuclears and 31 per cent lymphocytes. The urine had a specific gravity of 1.030 and no albumin or sugar was noted. The microscopic examination was negative. Kahn reaction was negative. The sedimentation rate was 5 mm. per hour (Cutler method). The blood sugar, urea nitrogen, chlorides and Van den Bergh were normal.

The admission diagnosis was myositis, but his condition did not improve on bed rest and salicylates. During the first week of June he complained of anorexia and abdominal cramps. His temperature ranged from 99° F. to 100° F. by mouth. The

sedimentation rate was then 44 mm. per hour and the white cell count had risen to 10,400 with a normal differential. The patient reported that one urine specimen was dark and smoky but the sample had already been discarded. Some nodules were felt along the course of the brachial arteries. A biopsy of the right biceps was done with negative findings.

Although he had no cardiac symptoms, an electrocardiogram was made which showed low T waves in Leads I and III. This was interpreted as suggesting myocardial damage. A clinical diagnosis was made of periarteritis nodosa although the biopsy had failed to confirm it.

Early in July he complained of numbness of both legs, and it was noted that he had foot drop on the left and decreased sensation to all modalities below the knee bilaterally, more marked on the left. On August 9, he had a generalized convulsion and the fundi showed papilledema. He fell out of bed and suffered contusions about the face. This event was one of the factors that led the neurosurgeon, at a later date, to consider the possibility of a subdural hemorrhage to account for certain of his neurologic findings.

The blood pressure on August 10 was found to be 220 mm. Hg systolic and 140 mm. diastolic. The spinal fluid showed 40 white cells per cubic millimeter, of which 70 per cent were polymorphonuclears and 30 per cent were lymphocytes. The Pandy and Kahn tests were negative but the colloidal gold curve was 5554321000.

The patient became more confused and dull and complained of severe frontal headaches. He was transferred to Tilton General Hospital on August 13, because of the possibility of an expanding intracranial lesion. A bilateral occipital trephination was done on August 15 with negative findings.

At that time the white cell count was 10,200 with 63 per cent polymorphonuclears of which 8 per cent were young forms, 28 per cent lymphocytes, 6 per cent eosinophiles, 2 per cent monocytes and 1 per cent basophiles. The specific gravity of the urine was 1.022 and a trace of albumin was found. There were a few casts and white cells present per high power field. The blood chloride level was 373 mg. per cent but the other chemical constituents of the blood were normal. The electrocardiogram showed low voltage of the T waves in Leads I and II and slight inversion in Lead III. A muscle biopsy done on August 15 showed normal findings.

His history of having worked as a painter led us to consider the possibility of plumbism as the most likely diagnosis after periarteritis nodosa since this condition could explain the cramps, vomiting, hypertension, foot drop and convulsions. The fact that he had been away from his occupation for more than one and a half years did not exclude the diagnosis. He had, partly by choice, been on a low calcium diet which would tend to mobilize any stored lead from the bones into the blood. There was some stippling of the red cells on one smear but no lead line was found on the gums. A twenty-four-hour urine specimen showed 12 gamma per cent of lead which was considered diagnostic of plumbism.

The patient continued a downward course and became more stuporous. On August 26 blood was found to be oozing from the right trephine incision and approximately 25 c.c. of dark blood and clots were expressed from the incision. The patient died on August 27.

The autopsy showed massive bilateral subdural hemorrhages which were considered as probably due to the trephine operation, a rather unusual complication. There were also old and recent pontine hemorrhages. The pia mater over the frontal lobes was fibrinous and thickened. The blood vessels of most of the organs studied showed varying degrees of inflammatory thickening, fibrinous degeneration, muscular disruption, vessel occlusion with recanalization and infiltration of the vessel walls with various inflammatory cells, lymphocytes, plasma cells, histiocytes, eosinophiles, and polymorphonuclear cells. The histologic appearance was characteristic of peri-

arteritis nodosa. The lesions were diffuse but patchy, and different stages of the process were observed, a few vessels showing acute inflammation but most of them showing the healing phase. The following organs were found to be involved: the heart (small coronary vessels), the liver, gall-bladder, spleen, pancreas, adrenals, kidneys, testicles, lumbosacral nerve plexus, and vessels of the brain.

Case 2. J. M., a white soldier, age 47, was admitted to Tilton General Hospital on August 19, 1942, complaining of pain in the abdomen, loss of weight, fever, pain in the legs, weakness and chronic cough since June 1942. The past history was irrelevant. His habits were not significant except that he smoked 20 cigarettes daily. Because of the history of abdominal complaints, positive guaiac test in the stools and the barium enema which showed poor filling of the descending colon, a diagnosis had been made of carcinoma of the descending colon at his previous station.

On admision he appeared emaciated, temperature was 99° F., pulse 130, respirations 20. The skin was pale, dry and scaly. There was moderate clubbing of the fingers and some ankle edema. The mouth was edentulous. He formerly had worn false teeth but had lost them during a bout of seasickness in January 1941 on his way to Newfoundland and had never attempted to acquire a new set. The heart was rapid and showed occasional premature contractions. No murmurs were heard. The blood pressure was 146 mm. Hg systolic and 78 mm. diastolic. An electrocardiographic tracing on the following day showed an iso-electric T wave in the first lead and inverted T waves in the second and third leads. Wheezes and rhonchi were heard in both lungs. The abdomen was scaphoid and no abnormal masses were felt. The liver was three fingers'-breadth below the costal margin. Neurologic examination showed diminished knee-jerks and absent ankle-jerks. There was a bilateral foot drop and glove and stocking hypesthesia of all extremities. The fundi showed changes of arteriosclerosis and small old hemorrhages in the left eye.

The urine had a specific gravity of 1.012 and contained one plus albumin (0.031 per cent), and 5 to 6 white cells per high power field. The blood chemistry values were essentially normal with the exception of serum albumin and globulin. The serum albumin was 2.8 grams per 100 c.c. of blood and the serum globulin was 3.24 grams. That ratio was maintained with minor variations throughout his illness. The red cells on admission numbered 4,600,000; the white cells numbered 12,800 with 70 per cent polymorphonuclears, of which 17 per cent were young forms, 27 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophiles. The white cell count was never markedly elevated, although on one occasion in December it reached 16,600. The maximum shift to the left of the Schilling index was 30 per cent young forms; the highest percentage of eosinophiles noted was 7 per cent. The blood sedimentation rate was 26 mm. per hour by the Cutler method and remained elevated throughout the illness. The spinal fluid obtained on September 4 was normal.

Roentgenograms of the chest were normal with the exception of congestive changes at the base of the lungs. The gastrointestinal roentgenograms and barium enema were normal. Gastric analysis showed absolute achlorhydria.

At first it was thought that his emaciation and peripheral neuropathy were due to vitamin deficiency since he had been without teeth since January 1941. However, he continued to have an irregular fever of 98 to 102° F., and failed to improve despite the use of massive doses of vitamins. Hence, on October 13, 1942, for the first time a diagnosis of periarteritis nodosa was made on clinical grounds. A biopsy of the left gastrocnemius muscle was done on October 21. The pathologist reported finding muscular degeneration and diffuse disease in the small arteries characterized by thickening and thrombosis with some perivascular infiltration with lymphocytes and histiocytes, which he stated would be compatible with the healing phase of periarteritis nodosa. A second biopsy of the gastrocnemius muscle was done three weeks

later and showed similar changes except that the vascular changes were more severe and appeared to be more inflammatory in character.

When the patient first came under observation he had hypostatic pulmonary congestion, enlargement of the liver, edema of the ankles, and markedly increased circulation time. The T wave was iso-electric in Lead I and inverted in Leads II and III. These signs and symptoms did not change following digitalization and bed rest. He had several transfusions which did not improve his condition materially. On November 23, he had severe pain and tenderness over the testicles which were relieved by sedation and the use of an adhesive support. On December 26 it was noted that he had petechiae on both arms and hands. The clinical course was progressively downward. A pericardial friction rub was heard on January 29. He developed pulmonary edema and died on January 30, 1943.

At autopsy the outstanding gross finding was marked wasting and atrophy of all body structures and viscera, except for the heart which showed moderate hypertrophy. Acute serofibrinous pericarditis was present as well as periarteritis nodosa of the smaller branches of the coronary arteries, with microscopic myocardial infarctions both old and recent.

Microscopically, vascular lesions of periarteritis nodosa were found widely disseminated; some of the vessels showed acute lesions whereas others showed the healing stage with thrombosis and recanalization. Infarctions were found in the liver and kidneys. The vessels of the peripheral nerves and of the testicles and prostate were found to be involved which adequately explained certain of the prominent clinical symptoms.

Case 3. F. M., a white male, age 26, was admitted to Fort Dix Station Hospital on April 15, 1942 with a complaint of generalized muscular aches and pains of four days' duration. On examination he had an injected throat and tenderness of the muscles around the elbows. The rest of the examination was negative. The heart rate was rapid and a soft systolic murmur was heard at the apex. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The electrocardiogram was normal. Roentgenogram of the chest was normal. The sedimentation rate was normal. Urinalysis showed a specific gravity of 1.026, no albumin or sugar, but some white and red blood cells. The blood count was 4,980,000 red cells with 90 per cent hemoglobin and 8,000 white cells (differential count not done). The blood chemistry including serum albumin and globulin was normal. The patient had a persistent low grade fever and the usual agglutination tests were negative.

On May 6, he complained of pain in the right testicle and burning pain on urination which subsided spontaneously in a few days. On May 17, he complained of chest pain and abdominal cramps and it was noted that he had lost 23 pounds. He also had numbness of the right first, second and third fingers and developed nodules on the medial aspect of the right arm and along the shins and ankles. He continued to show a septic type of fever and developed stiffness and numbness of the hands and feet. The red cell count was unchanged, but he now had a leukocytosis of 16,200 with 81 per cent polymorphonuclears and 19 per cent lymphocytes. The diagnosis of periarteritis nodosa was postulated and a biopsy of the right gastrocnemius was done which showed several thickened blood vessels infiltrated with polymorphonuclear cells and lymphocytes surrounded by fibrous tissue. One vessel, a vein, was thrombosed and partly recanalized. The pathologic diagnosis was made of periarteritis nodosa.

The temperature became higher and more irregular and the numbness in the extremities increased, particularly in the left foot. He complained of severe abdominal cramps and pain in the elbows and ankles. On June 12, he became cold, clammy and nauseated and had pin-point pupils. Tympanites developed, the pulse became imperceptible, and he gasped for breath. Death occurred that evening.

At autopsy the immediate cause of death was found to be acute massive subcapsular hemorrhage of the left kidney and the right lobe of the liver. The heart was normal. The lungs showed moderate hypostatic congestion. There were several sharply outlined areas of hemorrhage in the spleen. There were lesions characteristic of periarteritis nodosa in the smaller blood vessels of the diaphragm, the ileum, liver, spleen, pancreas and kidneys.

Summary

Three cases of periarteritis nodosa diagnosed during life and confirmed at autopsy are reported. The clinical features and differential diagnosis are discussed. The diagnosis should be considered in patients with prolonged fever of unknown origin who have irregular and baffling symptoms referable to many systems of the body. A biopsy of any readily accessible tissue such as the gastrocnemius muscle will usually reveal characteristic changes in the smaller arteries. Negative findings do not eliminate the possibility of periarteritis nodosa.

The etiology of the disease is unknown though it seems likely that the disease occurs as an allergic reaction to many different antigens, the arterioles being the shock organ. There is no specific treatment. Most of the well advanced and recognizable cases end fatally.

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AN ELECTROCARDIOGRAPHIC STUDY OF CARDIAC AGING BASED ON RECORDS AT REST AND AFTER EXERCISE *

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IT is often assumed that changes in the heart accompanying the aging process may be mirrored by the electrocardiogram, and that tracings in aged individuals should be interpreted with less rigid criteria than in the young. There is actually little evidence to support this view. Most of the studies which purport to show more electrocardiographic abnormalities in the later age groups are based on either "non-cardiac hospital patients" or on series of routine tracings of inadequately studied individuals. The careful study of Larsen and Skulason [1] avoided most of the sources of error of previous investigations. In a group of 100 normal persons divided equally between the fourth and fifth decades they found little evidence for cardiac aging. The only statistically significant differences between the two age groups were the greater frequency of a saddle-shaped S–T segment and left axis deviation in the older. It must be noted that the age difference between the two groups was only 10 years.

It has been thought that the imposition of a strain upon the heart might bring out electrocardiographic evidence of latent myocardial damage, and there is experimental support of this view.[2] In the main two methods have been used for the imposition of such strain, namely, oxygen deprivation and exercise. Because the rebreathing method used in the initial investigations [3, 4] induces an altering and uncontrolled degree of oxygen deficiency, Levy, Barach and Bruenn [5] devised an apparatus capable of providing a constant proportion of oxygen in the inspired air. In this and another study [6] Levy and his associates showed that oxygen deficiency so induced could cause T-wave depression and S–T segment deviation in normal individuals. Since the effects were often greater in patients with evidence of coronary insufficiency they set up criteria for a normal response, suggesting the use of the method as a test for coronary insufficiency. Larsen [7] published the results of a similar study.

Burnett, Nims and Josephson [8] administered a 10 per cent oxygen mixture (at the altitude of Denver, Colorado) to normal subjects between 21 and 60 years of age but were able to show no significant differences in the electrocardiographic responses in the various age groups. In brief, no evidence for the existence of cardiac aging was demonstrated by this method.

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From the Cardiovascular Research Unit, Veterans Administration Facility. Published with the permission of the Medical Director of the Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

In an earlier publication, May [9] had reported that "the effect of oxygen deficiency, as measured by diminution in the height of the T-waves, lessens considerably with advancing age." The validity of May's conclusion has been questioned by Burnett and his associates.[8] Since he used the rebreathing method May was not able to state the degree of oxygen deprivation to which his patients were subjected, and in view of the fact that the metabolic rate is generally higher in younger individuals, it seems likely that his younger patients were subjected to greater anoxic stress than the older.

The effects of exercise on the electrocardiogram of normal individuals have been studied,[10, 11, 12] and the response of the T-waves and S–T segments described. The degree and frequency of electrocardiographic change produced by exercise are generally greater in patients with diseased hearts. This method has apparently not been used to study cardiac aging.

The present study had two objects: first, to determine whether the electrocardiographic exercise response would give evidence of cardiac aging, and second, to establish standards for the electrocardiographic response to exercise in a sufficient number of normal individuals.

Experimental Subjects

All of the subjects were men. The younger group consisted of 44 young adults who were applicants for the position of U. S. Border Patrolman. They ranged in age from 21 to 33 with an average of 24.8 years. Because of the standards of the examination the minimum height was 68 inches; the maximum was 75.25 inches with an average of 70.5. The weight range was 132 to 223 pounds (average 170).

The older group consisted of 44 veterans of World War I who were applicants for U. S. Government Life Insurance. They varied in age from 39 to 56 years (average 46), in height from 63 to 73 inches (average 67.4) and in weight from 112 to 219 pounds (average 158).

Each individual was subjected to a complete history and physical examination. In addition, a urinalysis, blood Wassermann and Kahn tests, and a teleroentgenogram of the heart were done in each case. Only individuals who were normal by these criteria and whose resting blood pressures were below 150 systolic and 90 diastolic were included. Because of the nature of the examinations for which they were applicants, it was realized that there might be reticence in the free disclosure of symptoms on effort. An attempt to elicit such symptoms was made by a discussion of extravocational interests, hobbies and recreational activities of an athletic nature. Moreover, each individual was subjected to a two-step exercise test without producing unusual symptoms.

Technic

The records were made on a vacuum tube amplifier-oscillograph type of instrument. The sensitized paper was run at the standard rate of 25 mm.

per second and the instrument standardized for a deflection of 1 cm. per millivolt. The timer was checked and found to be running 1.5 per cent slow. Records were taken from the three standard limb leads and one chest lead, CF–4, with the patients lying supine. The chest electrode was circular and 3 cm. in diameter. Its position on the chest was marked so that it might be accurately reapplied after the exercise. The patients were exercised with the limb electrodes in place, the lead connections being disconnected. As soon as the exercise was completed the patient resumed his former position on the table. The lead connections were made and Leads IV, I, II and III were taken in order. The electrocardiograms were recorded within three minutes of the cessation of the exercise. The exercise consisted of ascending and descending a standard two-step staircase as many times as each patient was able within 90 seconds. The average number of trips was 41.8 in the younger group and 35.2 in the older. No patient made fewer than 30 trips, none more than 48.

The readings were made from the records with the aid of a magnifying glass whenever necessary. The height of several waves in each lead was measured to the nearest 0.025 mv. or one quarter of the smallest voltage unit on the tracings. The time intervals were measured to the nearest 0.01 sec. In cases where the voltage varied phasically, due to respiratory movements, the range was recorded and the average computed.. In cases in which sinus arrhythmia was present the longest and shortest R–R interval with their corresponding QRS and QT intervals were noted and averaged. The electrical axis was determined for each record by plotting the R and S waves in Leads I and III on the Einthoven triangle in the usual manner.

Results

The Electrocardiogram at Rest. A comparison of the electrocardiograms of the two age groups taken at rest reveals few significant differences. Sinus arrhythmia was somewhat more frequent in the younger group. The P-waves and P–R intervals were not significantly different. Discernible Q-waves in Leads I and II did not occur with significantly greater frequency in either group. A discernible Q-wave in Lead III occurred in 28 records of the younger group and in 17 of the older, a difference which the chi-square test indicates is statistically significant. The greater frequency of Q-waves in Lead III in the younger group is probably due to the greater tendency to right axis deviation in the group.[12] There was only one Q-wave in Lead III that was significantly deep by Pardee's criteria.[13] It was found in an older subject with a transversely placed heart and since its depth varied with respiration it is probably of no significance.[14] The average R-wave was of lower voltage in Lead I and of higher voltage in Leads II and III in the younger than in the older group. Related to this was the greater tendency to a "rightward" electrical axis (Einthoven) in the younger group. The average angle for this group was 59.0°, with a standard deviation of ± 23.5.

In the older group the average angle was 42.8° ± 27.3. The difference is statistically significant. There was no significant difference between the two groups in the duration of the QRS complex.

Elevation of the S–T segment of 0.5 or more in the limb leads occurred in five instances, all in Lead II in the younger group. Depression of the segment below the isoelectric line was never more than 0.5 mm. The frequency of S–T interval depression was not significantly different in the two groups. As shown in table 1 the average height of the T-wave was greater

TABLE I

Height of T-Waves before and after Exercise

Leads	Younger Group		Older Group	
	Before Exercise	After Exercise	Before Exercise	After Exercise
I	2.12	1.85	1.77	1.39
II	2.84	3.23	2.32	2.47
III*	1.37	1.66	1.16	1.38
CF-4	4.69	5.45	4.40	5.24

* Cases in which waves are positive.

in the younger group in each of the four leads, but only the differences in Leads I and II are statistically significant. The greater height of the T-wave in Leads I and II in the younger group assumes even greater significance when it is recalled that the electrical axis in this group was more "rightward" than in the older. The Q–T interval was not significantly different in the two groups. A linear formula was fitted to the entire data by the method of least squares after correction for the — 1.5 per cent error in the timer. The formula was

$$QT = 0.15 \times R\text{–}R \text{ plus } 0.22$$

The Electrocardiogram after Exercise. A. The Effects of Exercise within Each Group.

Sinus arrhythmia first appeared after exercise in two cases in the younger group and in six in the older. In the 13 records in the younger group in which it was present at rest it disappeared after exercise in five. It persisted after exercise in the one case in the older group.

The changes in the P-wave due to exercise were not significantly different in the two groups. It often decreased in voltage in Lead I and increased in Leads II and III. The maximum increase was 1.25 mm. Inversion of the P-wave after exercise occurred only once in Lead I and no times in Lead II. Changes in direction were frequent in Leads III and CF–4.

The P–R interval usually decreased in each lead in both groups after exercise. The decrease was generally greatest in Lead IV. This is probably due to the faster rate in this lead since it was the first taken after exercise.

The QRS complex was almost always diphasic or triphasic both before and after exercise. The monophasic complexes which did occur were always upright. The presence of discernible Q-waves was not markedly affected by exercise. A significantly deep Q-wave in Lead III was seen in two records after exercise; in one it had also been present at rest. Statistically significant changes in the voltage of the R-wave due to exercise occurred only in Leads I and CF–4 in each group. In both groups the waves became lower in voltage in both of these leads.

The average electrical axis in the younger group became more "rightward" after exercise. Changes of more than 5° to the right were seen in 32 cases and to the left in one. In the older group changes in both directions were common. Eighteen cases became more "rightward" and 14 more "leftward." The average change for the group was not significant.

The changes in the average duration of the QRS complex were minimal. It appeared to increase slightly in the limb leads and decrease slightly in the chest lead, but the changes were too small to be considered significant.

Depression of the S–T segment by exercise to below the isoelectric line from an initially positive or isoelectric position was seen in one or more limb leads in 49 tracings of the entire series. It was most often seen in Lead II, 33 times. In the chest lead it occurred in nine records. In the limb leads the S–T segment depression was greater than 0.75 mm. in only one record. In CF–4 the depression was greater than 0.75 mm. in seven cases; the greatest depression was 1.75 mm. Most often the depression in each lead was 0.25 mm.

T-wave inversion in either Leads I, II and CF–4 occurred only once after exercise. A T-wave in Lead I of 4 mm. became — 0.25 mm. after exercise. There was no reason to question the normality of this subject. The single diphasic T-wave in CF–4 became upright after exercise. Changes in T-wave voltage of 0.5 mm. or more occurred frequently in those leads in which T is normally highest, namely, Leads II and CF–4. Most often T_1 became lower in voltage while $T_{2, 3}$ and $_4$ became higher. The changes in Leads I and III were generally reciprocal in any one record. The average voltage of the T-waves before and after exercise in each group is given in table 1. The T-wave in Lead I appeared to become lower in voltage while those in Leads II, III, and CF–4 became higher after exercise. These changes are statistically significant in each instance except for T_2 in the older group. The statistical analysis was performed by solving for t by means of Fisher's method [15] for a unique sample. It is interesting to note that the average T-wave changes were opposite in direction in Leads I and CF–4.

The Q–T interval after exercise altered with the increase in rate. However, a linear formula fitted to the after exercise data by the method of least squares did not differ significantly from that for the control tracings.

B. Comparison of Changes in Younger and Older Groups.

The magnitude of the changes in the electrocardiograms due to exercise were compared in the younger and older groups by the appropriate statistical methods. The change in the voltage of the various waves was considered significant when the mean difference between the two groups was more than twice the standard deviation of their means. The frequency of various changes was compared by applying the chi-square test to a fourfold table. Differences giving a chi-square of more than 3.8 were considered significant.

The changes in the components of the electrocardiogram due to exercise were generally of the same order of magnitude in the younger and older groups. In only a few components were the differences between the two groups statistically significant. The changes due to exercise in the younger and older groups were not significantly different in respect to the duration of the P–R and QRS intervals, the P- and T-waves, and the R-waves in Leads I, III and CF–4. In Lead II the decrease in voltage of the R-waves in the younger group was significantly greater than in the older. The frequency of S–T segment depression in one or more of the limb leads was significantly greater in the older group. Such S–T segment depression was seen in 35 records of the older group and in 14 of the younger. The changes in the T-wave due to exercise were not significantly different in the two groups.

Discussion

The present study demonstrates but few significant differences between the electrocardiograms of males in the third and fifth decades. In tracings taken at rest significant differences between the two age groups were found only in the frequency of Q-waves in Lead III, the voltage of the R-waves in the limb leads, and the voltage of the T-waves in Leads I and II. The Q- and R-wave differences are to be related to the greater tendency to "rightward" deviation of the electrical axis in the younger group. The difference in electrical axis is probably due to a difference in the position of the heart. It should be noted the average height was less in the older group. The smaller height of the T-waves in Leads I and II in the older group must be considered to be indicative of cardiac aging, since any T-wave differences due to the variation in the electrical axis should be in the opposite direction. The analysis of the records secured after exercise gives additional evidence for cardiac aging. Significant S–T interval depression occurred more often in the older age group.

Both of these differences, namely, the lower T-waves in Leads I and II and the greater frequency of S–T segment depression, are considered evidence of a lessened myocardial efficiency in the older subjects as compared with the younger. The known effect of myocardial disease on the T-wave and S–T segment supports this view. In addition, the administration of oxygen which may be presumed to increase myocardial efficiency, often increases the voltage of T-waves in normal subjects.[16] The studies on oxygen

deprivation and exercise cited above have shown that S–T segment depression is one of the characteristics of coronary artery disease.

One of the primary purposes of the present study was to establish criteria for a normal response of the electrocardiogram to standard exercise. It is obvious that if such a test is to be useful in the recognition of coronary insufficiency, the complete range of response of the normal individual must first be known. It has been found in the present study that though the alterations in the QRS complex due to exercise show definite average trends, there are individual variations in either direction. Hence, definite criteria for the normal variation of this component cannot be established. With the S–T segment the situation is quite different. The changes after exercise were more constant and the variations from the average were small. Except for the T-wave in Lead I in one case, all of the T-waves in Leads I, II and IV were upright after exercise. Low voltage of the T-waves in all of the limb leads or in the chest lead was not seen after exercise.

From the data of the present study the following criteria for an abnormal electrocardiographic response to standard exercise in the age groups considered are suggested:

(1) Depression of the S–T segment by exercise of more than 0.75 mm. in Lead I, 1.5 mm. in Lead II, 0.75 mm. in Lead III, and 1.75 mm. in Lead CF–4.
(2) Inversion of the T-waves in Leads I, II or CF–4.
(3) Low voltage of the T-waves in all of the limb leads.

Criteria 1 and 2 would appear to be the most useful and dependable. The criterion for the S–T interval depression is based on the extreme depression seen in this series. Application of the statistical method with a range of three times the standard deviation from the mean gives substantially the same values as the extremes. Since, in general, the greatest degree of depression occurred in those cases in which the segment was slightly elevated initially, the final deviation after exercise was slightly less than the extremes given above. The criteria for the S–T interval change in this study are slightly more rigid than in that of Twiss and Sokolow.[12] It must be noted, however, that the "normals" in their study apparently included patients with heart disease (though not angina pectoris).

Summary

The changes in the normal heart due to aging have been investigated by comparing the electrocardiograms taken at rest and after exercise in 88 normal men divided equally between the third and fifth decades. The data were treated by appropriate statistical methods and the significant differences between the two age groups determined. The differences which are considered evidence of cardiac aging are noted and discussed. Criteria are suggested for the electrocardiographic response to standard exercise in normal subjects.

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LEUKOCYTOSIS AND THE SYMPATHETICO-ADRENAL SYSTEM *

By F. B. CLARE, C. H. CRESS, and E. GELLHORN,† *Chicago, Illinois*

ALTHOUGH leukocytosis has often been linked with the excitation of autonomic centers and the secretion of epinephrine (Müller,[1] Hoff [2]) actual proof for this mechanism is rather inadequate. Walterhöfer [3] showed that injection of epinephrine was followed by a neutrophilic leukocytosis which he attributed to the action of epinephrine on the bone marrow (cf. also Schön [4]). Borchardt [5] likewise observed leukocytosis after epinephrine, but the physiological evaluation of these experiments is doubtful since this effect occurs only after administration of large doses of epinephrine and since similar effects may be obtained also after the injection of parasympathetic stimulants such as pilocarpin and choline.

Several investigators have presented evidence that leukocytosis may follow stimulation of various parts of the central nervous system. Thus, Gotch [6] observed leukocytosis after injury of the corpus striatum, the thalamus and hypothalamus. Similar experiments were recently reported by Hayashida (cited after Hoff [7]). Injection of air into the ventricle of one partner of parabiotic rabbits was followed by a leukocytosis in the second partner suggesting that hormonal factors were involved (Beer [8]). Rosenow [9] and Foa and Roizin [10] likewise observed leukocytosis after stimulation of the ventricles of the brain. These findings, as well as the observation that cold (Harlow and Selye [11]) causes leukocytosis, are compatible with the assumption that leukocytosis is the result of an excitation of the sympathetico-adrenal system.[12] To prove this hypothesis, experiments were performed in which on normal and adrenodemedullated rats various procedures were employed which, according to our earlier work,[13] led to a stimulation of the centers of the sympathetico-adrenal system.

Method. The effect of convulsions induced by metrazol (50 mg. per kg. subcutaneously) and electroshock (Kessler and Gellhorn [14]), as well as the action of paratyphoid vaccine (Feldman and Gellhorn [15]), was studied on vagotomized and adrenodemedullated rats weighing 250 and 300 grams. Vagotomy was performed abdominally [13] in order to eliminate the vago-insulin system which is activated by these procedures together with the sympathetico-adrenal system, as our blood sugar studies indicated. Changes in blood count observed in vagotomized rats are attributable to the excitation of the sympathetico-adrenal system whereas changes occurring in adrenodemedullated rats indicate an involvement of the vago-insulin system. The food was removed 10 hours before the experiment, and blood was obtained

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from the tail after at least three drops had been discarded. Neubaur improved hemocytometers with standardized pipettes were used.

Following the operation at least two weeks were allowed to pass to offset the effects of the surgery and any low grade infections. Initial leukocyte counts over 25,000 were considered abnormal, in the light of the findings of previous workers (Farris [16]), and the animals were not used.

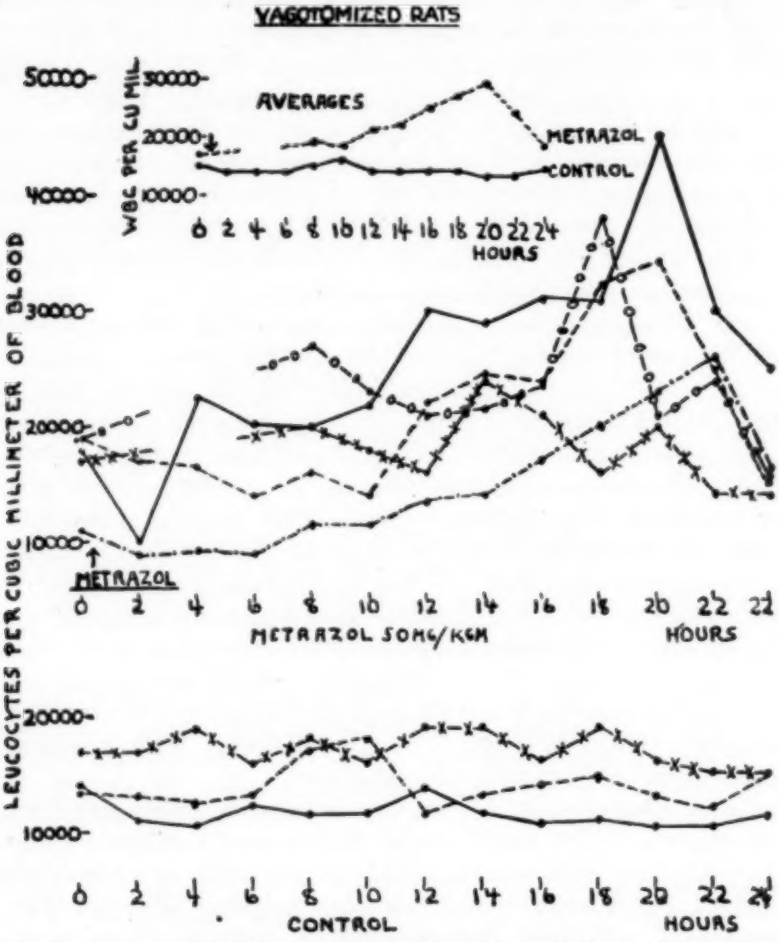

FIG. 1. Lower part. Control experiments show the variation in leukocyte count in three vagotomized rats. Samples were counted at two hour intervals for 24 hours. Middle part. Effect of metrazol convulsions (50 mg. per kg.) on the leukocyte count of vagotomized rats. Upper part. Averages of control and metrazol experiments.

Samples were taken over a 24 hour period in three vagotomized and three adrenodemedullated rats. In two of these, they were taken every hour. In the remainder they were taken every two hours.

Results. Bi-hourly leukocyte counts for a period of 24 hours showed only slight changes in three vagotomized and three adrenodemedullated rats

(figures 1 and 2). No significant changes in differential count were found. The erythrocyte count was decreased about 10 per cent at the end of the 24 hour period.

After the injection of metrazol leading to typical convulsions, blood counts were taken for 24 hours. In all vagotomized rats a considerable leukocytosis was observed with a maximum occurring approximately at the

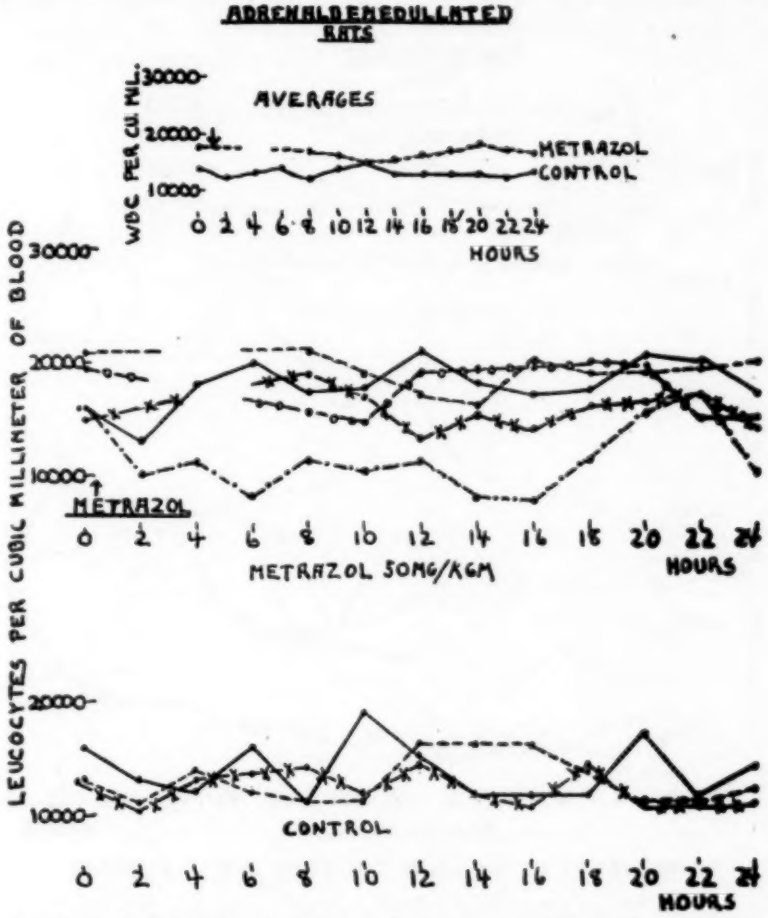

FIG. 2. Controls and metrazol effects on the leukocytes of adrenodemedullated rats. Arrangement as in figure 1.

eighteenth hour, whereas the leukocytes remained unchanged in the demedullated group in spite of the fact that both groups reacted with convulsions of similar character. At the top of figures 1 and 2 are given the averages of the control and experimental groups showing that leukocytosis after metrazol convulsions is confined to the group in which the adrenal medullae are intact. The maximal increase in leukocytes in the vagotomized groups varied between 44 and 232 per cent (average 120 per cent), whereas the va-

riation in the adrenodemedullated group was between 0 and 28 per cent (average 15 per cent). This increase in the number of circulating leukocytes is apparently due to a marked increase in the neutrophilic leukocytes since they showed an average increase of 100 per cent in the vagotomized group but only of 19 per cent in the adrenodemedullated group.

The presence of changes in the leukocyte count in the vagotomized animals, the absence of these changes in the adrenodemedullated rats, and the

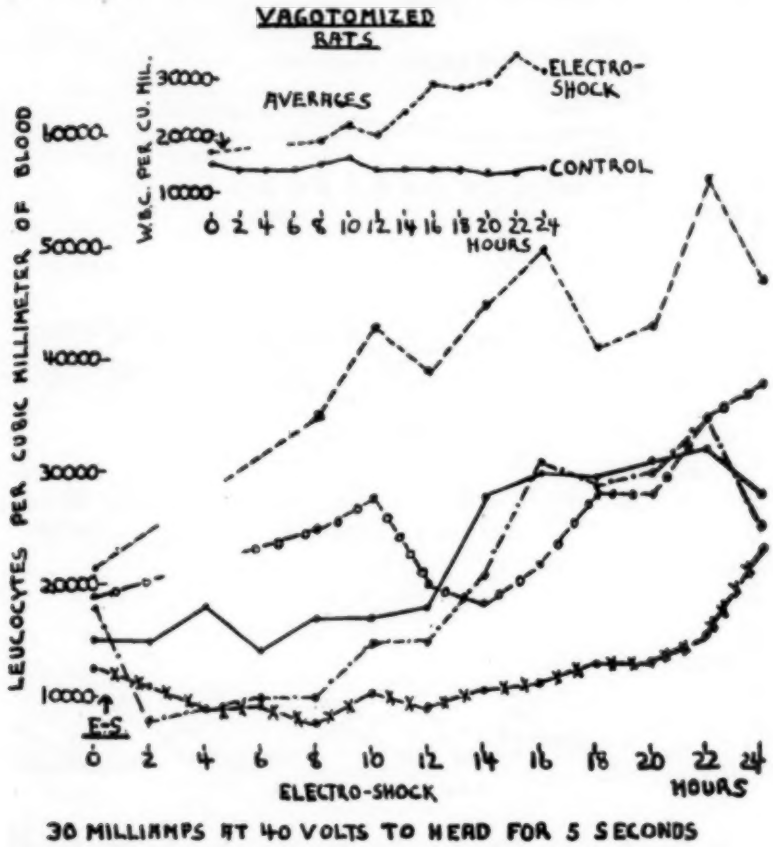

FIG. 3. Effect of electrically induced convulsions on the leukocyte count of vagotomized rats.

absence of changes in the erythrocyte count in both groups eliminate the possibility of the leukocytosis being on a concentration-dehydration basis.

The effect of electrically induced convulsions on the leukocyte count was similar to that discussed for metrazol convulsions. All the vagotomized animals showed a marked increase, whereas the adrenodemedullated rats showed no significant change. This is illustrated in figures 3 and 4. The averages compared with those of similar animals under control conditions are again represented in the half-size insert graph.

The average maximal percentage increase in the leukocyte count above the initial value for vagotomized rats was 110 per cent. The adrenodemedullated rats had an average increase of only 25 per cent. Neutrophiles showed on the average an increase of 50 per cent in the former and a decrease of 6 per cent in the latter.

Erythrocyte counts taken at the height of the leukocytosis showed no appreciable changes.

It is evident that the leukocytosis following metrazol and electro-shock convulsions is eliminated by adrenodemedullation.

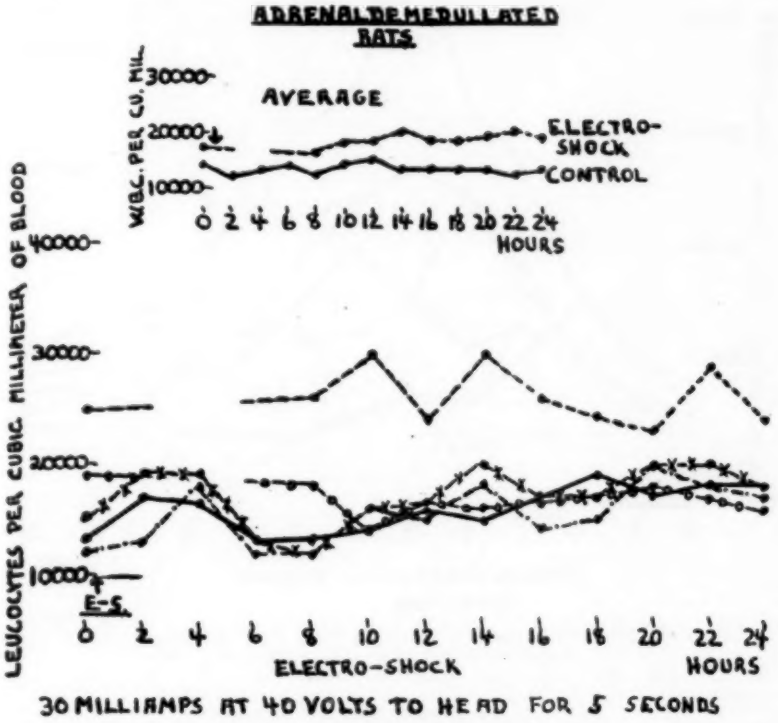

FIG. 4. Effect of electrically induced convulsions on the leukocyte count of adrenodemedullated rats.

Results of typhoid-paratyphoid vaccine injections were not so clear cut. All of the 10 rats studied, vagotomized and adrenodemedullated alike, developed a marked leukocytosis after the injections. There was a slight decrease in the erythrocytes as shown by counts taken at the beginning and end of the experiments. Differential counts suggested a leukocytosis of neutrophilic origin.

Figures 5 and 6 illustrate the individual records of these rats. In general it may be noted that the peak of the leukocytosis occurred in about 10 hours, whereas in the cases previously discussed it took place after 18 to 20 hours. Adrenodemedullation does not eliminate the leukocytosis following

typhoid-paratyphoid vaccine, although it appears to alter its characteristics. The vagotomized rats showed a steady and consistent increase followed by a return to normal whereas the curve was rather irregular in the adrenodemedullated group.

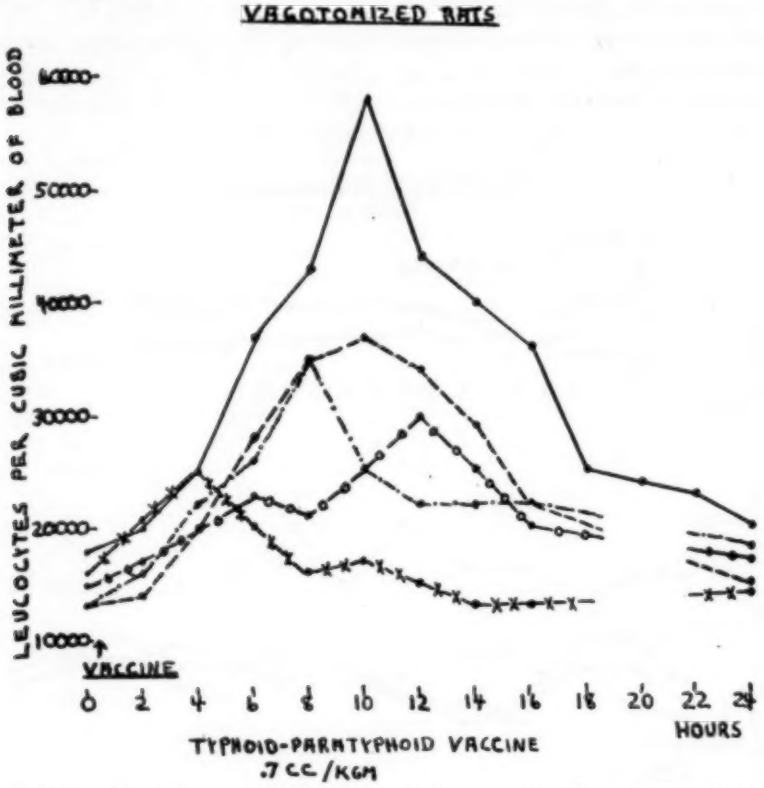

FIG. 5. Effect of typhoid-paratyphoid vaccine (.7 c.c. per kg., intraperitoneally) on the leukocyte count of vagotomized rats.

DISCUSSION

The fact that leukocytosis occurs after electrically or chemically (metrazol) induced convulsions in the vagotomized but not in the adrenodemedullated rats suggests that leukocytosis results from the liberation of adrenalin following excitation of sympathetic centers by these procedures. This interpretation is supported by previous studies which clearly showed that these convulsive procedures lead to an excitation of the sympathetico-adrenal system since the blood sugar rise is confined to the normal animals and does not occur in adrenodemedullated rats.[13] No evidence could be found in the present series for an influence of the vago-insulin system on the blood picture.

The relatively long latent period and persistence of the leukocytosis as well as its neutrophilic character points to the bone marrow as the site of action of the liberated epinephrine. If the increase in leukocytes were due to a contraction of the spleen, it would be expected that the leukocytosis

would occur after a shorter latent period and would be of brief duration. Moreover, it would be of a lymphocytic rather than a neutrophilic character. In addition, these latter forms of leukocytosis seem to be independent of the presence of the adrenal glands.

It appears very likely that this interpretation is applicable to man. The temporary increase in leukocyte count found by Low and collaborators [17]

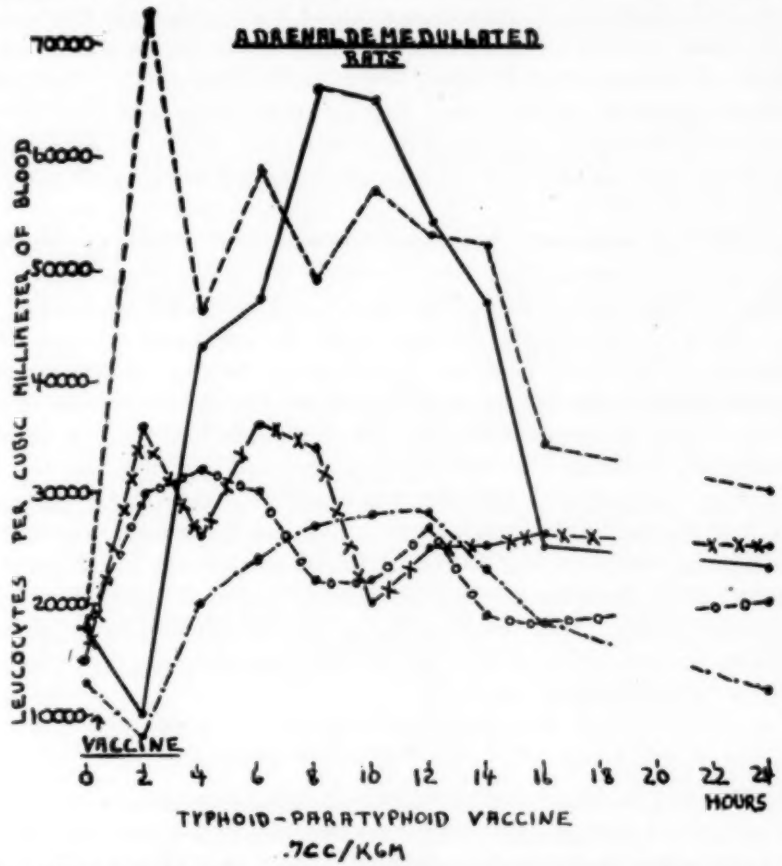

FIG. 6. Effect of typhoid-paratyphoid vaccine (.7 c.c. per kg., intraperitoneally) on the leukocyte count of adrenodemedullated rats.

after metrazol convulsions is probably due to a discharge of epinephrine. The identity of these changes with those found in our animals is made even more probable by the observations of Horn,[18] who demonstrated a neutrophilic leukocytosis in patients after metrazol convulsions. It is of interest to note that Horn attributed this effect to a stimulation of sympathetic centers in the midbrain.

The interpretation given to our experiments on leukocytosis following metrazol injections and the application of electro-shock involves the excitation of central autonomic centers with subsequent sympathetico-adrenal discharge. If this interpretation is correct, it should be possible to prove that

other conditions leading to a sympathetico-adrenal discharge likewise induce a leukocytosis. This is indeed the case as shown by our studies on the effect of various forms of anoxia on leukocytosis.[19] Furthermore, our interpretation presupposes that adrenodemedullation acts only by elimination of adrenalin secretion under conditions which lead to a stimulation of the sympathetico-adrenal centers. The fact that metrazol and electro-shock fail to cause leukocytosis in adrenodemedullated rats, although this effect is regularly observed when the adrenal medulla is present, as well as the observations of Walterhofer, Reicher, Borchart, and Schon that the injection of adrenalin produces a leukocytosis, further substantiates our hypothesis.

Our interpretation is likewise applicable to the studies of Milhorat[20] as well as Mora and collaborators[21] who observed leukocytosis as a result of emotional excitement.

The preceding discussion has clearly shown that the leukocytosis following metrazol and electro-shock convulsions is due to a sympathetico-adrenal discharge. Other conditions such as anoxia and emotional excitement which lead to a sympathetico-adrenal discharge may likewise cause a leukocytosis in this manner. There are, however, complicating factors. Our experiments on typhoid-paratyphoid vaccine injections have clearly shown that the sympathetico-adrenal discharge which is well established under these conditions (Gellhorn and Feldman) is not the only factor responsible for the leukocytosis, since vagotomized and adrenodemedullated rats showed this effect to a similar degree. The leukocytosis cannot be the consequence of fever, since Feldman, Gellhorn, and Cortell[15] found an increase in temperature in the normal and a decrease in the adrenodemedullated animals after typhoid-paratyphoid vaccine. The results suggest that the typhoid-paratyphoid vaccine acts on the bone marrow directly, possibly in addition to the action of the vaccine on the sympathetic centers.

Summary

The effect of metrazol and electrically induced convulsions as well as the action of typhoid-paratyphoid vaccine on the leukocyte count was studied in vagotomized and in adrenodemedullated rats. The abdominal vagotomy served to eliminate the vago-insulin system. It was found that convulsions caused by metrazol and electro-shock caused in every vagotomized rat a neutrophilic leukocytosis reaching a maximum in 18 to 24 hours and averaging 115 per cent. No leukocytosis was found in adrenodemedullated animals. It is concluded that the leukocytosis following metrazol and electro-shock convulsions is due to a sympathetico-adrenal discharge. The epinephrine secreted is believed to act on the bone marrow.

Typhoid-paratyphoid vaccine produces leukocytosis in both vagotomized and adrenodemedullated animals with a maximal effect after 10 hours. The results appear to indicate that the paratyphoid vaccine exerts some direct action on the bone marrow which is responsible for the increase in the number of leukocytes.

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EXTRARENAL UREMIA: REPORT OF TWO CASES DUE TO PYLORIC OBSTRUCTION*

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Uremia is an anticipated complication of nephritis, obstructions to the urinary tract, and all degenerative and inflammatory diseases of the kidneys. In the absence of these diseases, it is less commonly found and less commonly searched for. The subject of extrarenal uremia is not new. As a complication superimposed upon an already serious medical or surgical disorder, however, its importance is great and its interest paramount. Two cases of extrarenal uremia treated at the Milwaukee County Hospital are reported here.

Case Reports

Case 1. A 56 year old, American born, white male entered the Milwaukee County Hospital the evening of February 21, 1942. The patient was awake and quiet, but disoriented and unable adequately to voice complaints. He had been suffering from nausea and vomiting of one month's duration.

In May of 1941, he had been operated on at a hospital in another city for a peptic ulcer. He left the hospital after an uneventful postoperative course and went to work in Michigan. From there he returned to Milwaukee two days before entrance to this hospital, and complained to his wife that for the past month he had been unable to eat without vomiting shortly thereafter. Since his return home, vomiting had occurred every time an attempt was made to take food or water; for that reason, very little had been ingested during the 48 hours prior to admission to the hospital. Twenty pounds in weight had been lost. Pain had not been prominent.

On examination there was found a middle-aged, white male, only moderately well nourished, grossly confused and somewhat lethargic. The patient's temperature was slightly subnormal, and was never remarkable until the terminal rise. Blood pressure was 105 mm. Hg systolic and 85 mm. diastolic. Essential features of the physical examination were moderate dehydration, soft and doughy abdomen without marked tenderness, adequate liver dullness, depressed peristaltic sounds, a right upper quadrant, paramedian, healed, surgical scar, and the presence of normal fecal material in the rectum. The eyegrounds were examined and nothing abnormal was found. No urine was obtainable on admission.

Several thousand cubic centimeters of parenteral fluids were given, and in the morning the patient appeared slightly better for a short time. Vomiting began, however, when ingestion of water was attempted.

A program of nothing by mouth was followed, with administration of 4,000 cubic centimeters daily of parenteral fluids in the form of normal saline and 5 per cent glucose. Hydration was still inadequate, and the patient's mental condition remained confused and poorly responsive.

Chemistry of the blood 36 hours after entrance to the hospital revealed: nonprotein nitrogen 226.5 mg. per 100 cubic centimeters; creatinine 4.0 mg. per 100 cubic

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centimeters; chlorides 340.0 mg. per 100 cubic centimeters; carbon dioxide combining power 78.0 volumes per 100 cubic centimeters.

Parenteral fluids were increased to 5,000 cubic centimeters daily, with 2,000 of 5 per cent glucose in saline and 3,000 of plain 5 per cent glucose. Blood pressure continued within normal limits. Spinal tap revealed only a slightly increased globulin content. After 60 hours there was no evidence of free flow of urine. At this time 500 cubic centimeters were obtained by catheterization. The next day, however, a total of 850 cubic centimeters was passed spontaneously, and was described as having many white blood cells. The next day an analysis revealed clear urine.

The urinary output never reached a maximum of more than 1400 cubic centimeters in 24 hours, in spite of forced fluids. The nitrogen of the blood dropped gradually to a non-protein nitrogen value of 89 mg. per 100 cubic centimeters and creatinine of 2.3 in nine days. Administration of 5 per cent ammonium chloride by proctoclysis was followed by a rise in the blood chloride to 472 mg. per 100 cubic centimeters and a drop of the carbon dioxide combining power to 60.7 volumes per 100 cubic centimeters.

Vomiting continued, in spite of nothing by mouth. The vomited material was clear and watery. The patient's breath became foul and uremic in odor. A soft pericardial friction rub was heard on one occasion.

On the seventh hospital day, blood sodium determination was found to be 277 mg. per 100 cubic centimeters and the potassium level 20. Blood plasma was given intravenously on this day and again two days later. The temperature began to rise about this time to a level of 102° F. rectally. Pneumonia was discovered the next day, and on this, the eleventh hospital day, the patient quietly died.

A report was obtained of the patient's illness of May 1941. Operation was done at that time for a ruptured duodenal ulcer, and recovery occurred after a relatively uneventful postoperative course. Urinalysis at that time revealed a straw colored fluid without albumin or sugar.

Postmortem examination by the Pathology Department of the Milwaukee County Hospital disclosed the following important findings: 1. *Gastric* ulcer with beginning malignant degeneration. 2. Fibrous, *almost imperforate,* pyloric stenosis. 3. Interstitial renal edema and tubular degeneration. 4. Terminal bronchopneumonia.

Case 2. A 52 year old white laborer, who appeared irrational, restless, dyspneic and dehydrated, was admitted to the hospital. He had vomited two or three times a day for the past five months and had lost 25 pounds during that time.

The patient had entered this hospital 10 months previously when a diagnosis of perforated peptic ulcer was made. A subdiaphragmatic abscess was drained, and after recovery, the patient was advised to have an operation for the ulcer. However, he refused this suggestion. In addition to these disorders, the patient stated that he had a congenital kidney condition which had caused symptoms for most of his life. Urinalysis revealed a 3 plus albumin, and many white blood cells. Red cells and casts were absent.

On the present admission the patient was emaciated and irrational. There was constant muscular twitching, but no convulsions. There was carpopedal spasm and a positive Trousseau sign. The head was essentially negative, but the mouth and tongue were dehydrated and blood clots were found in the right nostril. Chvostek's sign was positive. There was voluntary rigidity of the neck, but it was otherwise negative. No chest abnormalities were noted. The heart was normal with a rate of 96 beats per minute. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. The abdomen was scaphoid, with a two inch scar on the right medial costal margin. Rigidity of the abdominal muscles was present. No masses were palpable and the intestinal gurgles were hypoactive. Rectal examination was negative.

Urinalysis was negative except for the abnormalities noted before, namely a 3 plus albumin and numerous white blood cells. A blood count taken 24 hours after admission showed hemoconcentration and a leukocytosis of 17,000. The initial chemical studies of the blood indicated a marked azotemia and alkalosis with hypochloremia. The accompanying table gives a detailed report on the chemistry of the

Blood Chemical Changes before Operation in Case 2

	1st Hospital Day	2nd Hospital Day	3rd Hospital Day	4th Hospital Day
Nonprotein Nitrogen	96.7 mg. %	103 mg. %	66.6 mg. %	35.9 mg. %
Urea Nitrogen	50 mg. %	49.6 mg. %		
Creatinine	3.6 mg. %	3.4 mg. %	2.5 mg. %	1.5 mg. %
Sodium Chloride	240 mg. %	420 mg. %	480 mg. %	460 mg. %
Alkali Reserve	87 vol. %	69.2 vol. %	56 vol. %	
Uric Acid	7 mg. %	5.7 mg. %		3.1 mg. %
Total Protein	9.06 Gm. %	6.8 Gm. %	5.04 Gm. %	7.41 Gm. %
Albumin	5.9 Gm. %	5.0 Gm. %	3.7 Gm. %	4.65 Gm. %
Globulin	3.16 Gm. %	1.8 Gm. %	1.34 Gm. %	2.76 Gm. %

blood during the preoperative period. There was complete gastric retention at the end of four hours. Wangensteen suction was kept in operation from the fourth to the seventh hospital days. The clinical impression was peptic ulcer with cicatrization and pyloric obstruction with alkalosis and extrarenal uremia.

Four to 6 liters of normal saline were given parenterally every day for five days. On the ninth hospital day the chemical studies of the blood showed normal figures. On the tenth hospital day the patient was operated upon. Dense adhesions were found about the pylorus, liver, and duodenum. Posterior gastroenterostomy was done, but no attempt was made to resect the pyloric end of the stomach. The patient made an uneventful recovery and left the hospital on the thirty-first postoperative day on an ambulatory ulcer diet.

Discussion

Extrarenal uremia is a clinical state characterized by elevation of the blood nitrogen, dehydration due to loss of extracellular fluid and electrolytes, normal or low blood pressure, and oliguria which may progress to anuria. The primary responsible factors are extrarenal in origin. In the cases in which death occurs, structural changes in the kidney are either entirely absent or are of insufficient degree to account for failure of renal function. By definition are excluded from classification as causes of extrarenal uremia all infections or inflammatory renal diseases, tumors, strictures, anatomical variations or other obstructions at any place in the urinary tract, nervous imbalance or paralyses which prevent the normal excretion of urine, as well as serious damage to the parenchyma of the kidney from any cause.

The diseases in which a significant degree of retention of nitrogen in the blood has been found to occur most frequently are those in which dehydration is a prominent feature. Such dehydration may be caused most notably by excessive diarrhea, vomiting, insufficient intake of water, and diabetic acidosis. Nitrogen retention following massive bleeding into the gastrointestinal tract is due in part at least to digestion and absorption of blood protein.

Dehydration is induced by abnormal loss of extracellular electrolytes and water through the avenues of vomiting, diarrhea, diuresis, sweating or through a fistulous tract. In dehydration, the evidence of loss of fluid volume is confined chiefly to extracellular fluid. Extracellular fluid is characterized by its high content of sodium, chloride and bicarbonate, and small amounts of potassium, phosphate and magnesium. The patient discussed in case 1 had a low blood sodium value and a normal blood potassium value. Blood plasma, lymph, interstitial fluid and cerebrospinal fluid represent the chief sources of extracellular fluid in the body. Gastric juice, bile and the intestinal secretions are modified forms of extracellular fluid. Sweat and urine are also modified forms of extracellular fluid which are lost to the body normally within certain limits.

Cellular membranes separate the two components containing the extracellular and the intracellular fluid. Water is free to move between the two in response to osmotic forces. The effective osmotic pressure of these two components is due largely to concentrations of sodium and potassium respectively. The distribution of these two elements is a very important, if not the chief factor, in controlling the distribution of body water.

It has been suggested that the extrarenal uremia which supervenes upon high intestinal obstruction is due to hypochloremia. The error of this conception seems now to be clearly established, although depletion of blood chlorides may occur simultaneously. The error has been revealed by the production of hypochloremia in dogs through gastric lavage or vomiting, with, however, provision for sufficient food and water for the animals. No increase in non-protein nitrogen occurred in the blood until immediately before death, although the chloride content of the blood had fallen to half its normal level.

Prolonged dehydration resulting from upper intestinal obstruction has been shown to produce definite impairment of renal function in dogs and in man, as indicated by the excretion of both urea and phenolsulfonphthalein.

Disturbance of the circulation seems to be present without exception in extrarenal azotemia. In those cases with a salt deficiency, such as follows excessive vomiting, deterioration of the circulation is induced by dehydration. Loss of sodium leads to loss of water, and the latter takes place always at the expense of extracellular fluid. Consequently the amount of circulating blood diminishes and the blood becomes more concentrated. Owing to the reduced blood volume the circulation slows down, the blood pressure may fall, and the concentration of the serum involves increase of the colloid osmotic pressure of the blood. The decrease of the blood pressure and the increase of the colloid osmotic pressure together result in diminution of filtration pressure, the extent of which in severe cases can be so great that the pressure ceases to exist at all. Diminution of the blood flow is a further factor largely inhibiting glomerular filtration.

Deterioration of the circulation is significant not only from the point of view of renal function but from that of insufficient filling of the coronary arteries as well. Characteristic electrocardiographic changes in the ST segment, voltage and T waves, at times reversible, have been reported.

There is undoubtedly increased protein disintegration in states of azotemia induced by vomiting. This is not by itself sufficient to lead to lethal azotemia, however, because there are conditions, for example the infectious diseases, in which rather severe protein disintegration takes place but lethal azotemia does not follow as long as renal function is unimpaired.

In azotemia following hemorrhage the loss of blood leads to hemodynamic changes similar to those described. In congestive heart failure the slackened blood supply of the kidneys is due to diminution of cardiac output or to passive congestion. Excessive postoperative use of pitressin by its antidiuretic effect is said to contribute to nitrogen retention.

The presence of albumin and casts in urine does not necessarily indicate an irreparable kidney lesion. These urinary findings are frequent in cases of extrarenal uremia, and their disappearance usually coincides with the return of normal urinary flow and the fall in the level of blood nitrogen to normal.

Treatment of extrarenal uremia involves replacement of water, sodium and chloride, maintenance of the normal circulation and volume of the blood, and removal of the cause of the catastrophe. Shock if present must be combated and blood transfusion probably will be valuable. Restoration of extracellular electrolytes and water is accomplished by subcutaneous or intravenous infusions of sodium chloride or one of its modifications. Seven thousand cubic centimeters daily may be required. Where acidosis is present, adjustment of acid base equilibrium may be accomplished better by intravenous sodium lactate. For alkalosis the reduction of bicarbonate of the blood by oral or parenteral ammonium chloride, by intravenous administration of dilute hydrochloric acid, or simply by salt in the form of intravenous saline or hypertonic sodium chloride solution have all been recommended. Intravenous amino acids and blood plasma have been advised for hypoproteinemia. If food is tolerated, small feedings should be given every two hours consisting of 150 to 200 cubic centimeters of concentrated liquid or semi-solid carbohydrate food. Antispasmodics of the belladonna group are often of value in full therapeutic dosage. If nausea and vomiting are present, nothing should be given by mouth. Food which is regurgitated not only accomplishes no good, but actually does harm by increasing the loss of electrolytes in the gastric secretions. The same unfavorable result may be brought about by food when it aggravates severe diarrhea. When pyloric stenosis is present, the stomach should be aspirated at least once daily. Successful termination of azotemia which had been induced by pyloric obstruction of the type described has been brought about by gastrojejunostomy, which is favorably reported and recommended. Feeding of the patient through a jejunostomy prior to the gastrojejunostomy is recommended for

selected cases where uremia does not respond to parenteral fluids adequately for major surgical intervention.

Summary

Two cases of extrarenal uremia due to pyloric obstruction following long standing peptic ulcer are reported. One case recovered following operation, and the other died. At autopsy only insignificant renal damage, not sufficient to account for the uremia was seen. Beginning malignant degeneration was found in the ulcer area. A discussion of extrarenal uremia is given, and the etiology and importance of uremia of this type are stressed. Treatment is outlined.

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CASE REPORTS

CHYLOTHORAX; BRIEF REVIEW OF LITERATURE; REPORT OF THREE NON-TRAUMATIC CASES *

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CHYLOTHORAX, an effusion of chyle in the pleural cavity, holds our interest because it is a relatively rare condition, may be of obscure etiology and may have unusual pathologic lesions. According to Brescia,[1] Bartolet first described this entity in 1633, and Quincke [2] reported the first authoritative case in 1875. Yet, 56 years later, in 1931, Van Nuys [3] was able to collect but 66 cases of chylothorax of all types, and according to Nowak and Barton,[4] only 84 cases were reported up to 1937. Høyer,[5] who says it is an exceedingly rare condition, found no additional cases up to 1938 when he reported the eighty-fifth case, the first from Norway.

Since that date we have found reported in English 11 additional single cases by different authors: namely, Harrell, Street and Reiser,[6] and Everhart and Jacobs [7] in 1939; Gordon,[8] Cookson and Slade,[9] Cellan-Jones and Murphy [10] and Matson and Stacy [11] in 1940; Sullivan,[12] Brescia,[1] Nowak and Barton,[4] and Smith and Woliver [13] in 1941; and Dorsey and Morris [14] in 1942. Six other single cases are reported in foreign journals not available for review. The authors are as follows: Douady, Dupuy and Bouvrain [15]; Fujita, Bando and Sugishita [16]; Cercas [17]; Cziglány [18]; Lamartine de Assis and Raino [19]; and Foffani.[20] Adding these last six brings the total reported cases of chylothorax, at the present writing, to 102. To this group I wish to add three cases observed at the Henry Ford Hospital, none with associated trauma, making the total to date 105.

CASE REPORTS

Case 1. F. B., a white male, age 54, was first seen on March 6, 1939 because of swelling of the left arm and left side of the neck of six months' duration. Positive findings included a large, hard thyroid gland, possibly malignant; enlarged left anterior cervical and submaxillary glands; lymphedema of left arm and left cervical and upper chest regions; flat percussion note over the left lower chest; blood pressure 150 mm. Hg systolic and 90 mm. diastolic; and slightly enlarged prostate gland believed to be benign.

There was a history suggestive of coronary occlusion three years before this illness, but no confirmative evidence in the electrocardiographic tracing taken at this admission. There *was* evidence of arteriosclerotic heart disease.

Roentgenograms of the chest gave evidence of a collection of fluid in the left pleural cavity, but no mediastinal mass. There was slight widening of the upper mediastinum and the trachea was displaced slightly to the right.

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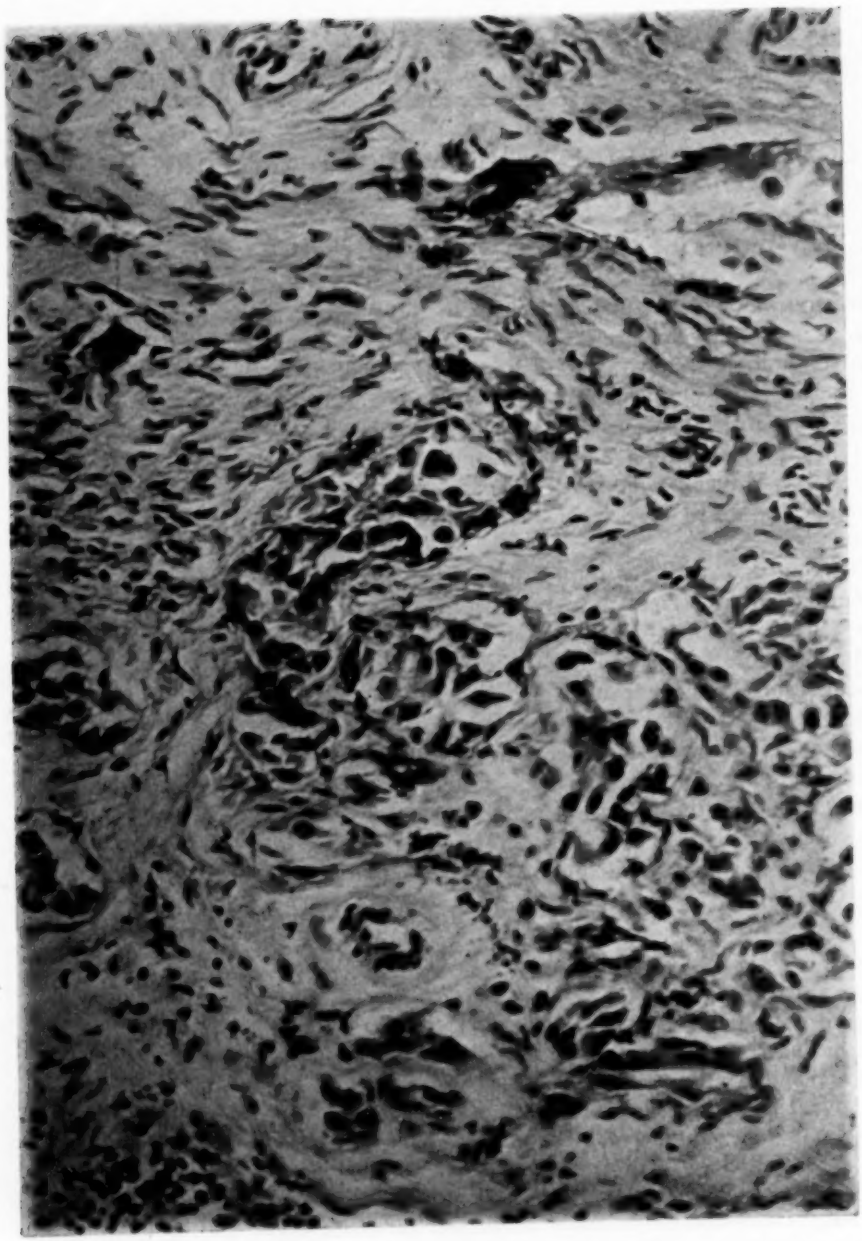


FIG. 1. Photomicrograph of section taken from cervical lymph gland of case 1. Lymphoid structure almost completely replaced by metastatic tumor growth, which is composed of small polyhedral epithelial cells arranged in atypical alveoli and in small solid masses and groups. Occasional mitotic nuclei present. Hematoxylin and eosin stain.

Aspirated pleural fluid was milky, sterile. It contained much fat and 950 mg. of protein per 100 c.c., and had a specific gravity of 1.014, thus meeting most of the criteria for true chylous fluid.

Biopsy of a neck gland was reported by the pathologist as metastatic carcinoma. A photomicrograph of the section of the gland is shown in figure 1.

Roentgen-ray therapy was given in small doses daily for several days. The patient seemed about as usual after his treatment on the twelfth day. He had talked with his nurse at 11:45 a.m. and at 12:20 p.m. was found dead in his chair.

At autopsy there was a fresh occlusion of the coronary artery at the site of advanced sclerotic changes. There was also evidence in the heart of previous myocardial infarction. Abdominal and pelvic lymph nodes, as well as mediastinal and cervical, were involved with metastatic carcinoma. There was a small area in the prostate gland suspicious in the gross of being malignant, and microscopic examination showed adenocarcinoma Type III.

Case 2. W. G., a white man, aged 64, first came for examination on March 14, 1940 because of dyspnea, anorexia and "gas" after meals, causing "pressure on the heart." There was some substernal distress on exertion, cough at times, and swelling of the ankles late in the day. He had lost 17 pounds in two months.

Findings: Weight still 20 pounds above ideal; some respiratory distress; flat percussion note over the left lower chest; a few moist râles at the right base; and mild pitting edema of the ankles.

The cardiologist felt that the symptoms and findings could be adequately explained by heart failure.

Roentgenograms of the chest showed moderate enlargement of the heart and aortic shadows. The hilus areas were considerably accentuated. There was marked increase in the bronchovascular markings throughout both lungs and evidence of some fluid in the left pleural cavity. There was a small area of pneumothorax at the left apex.

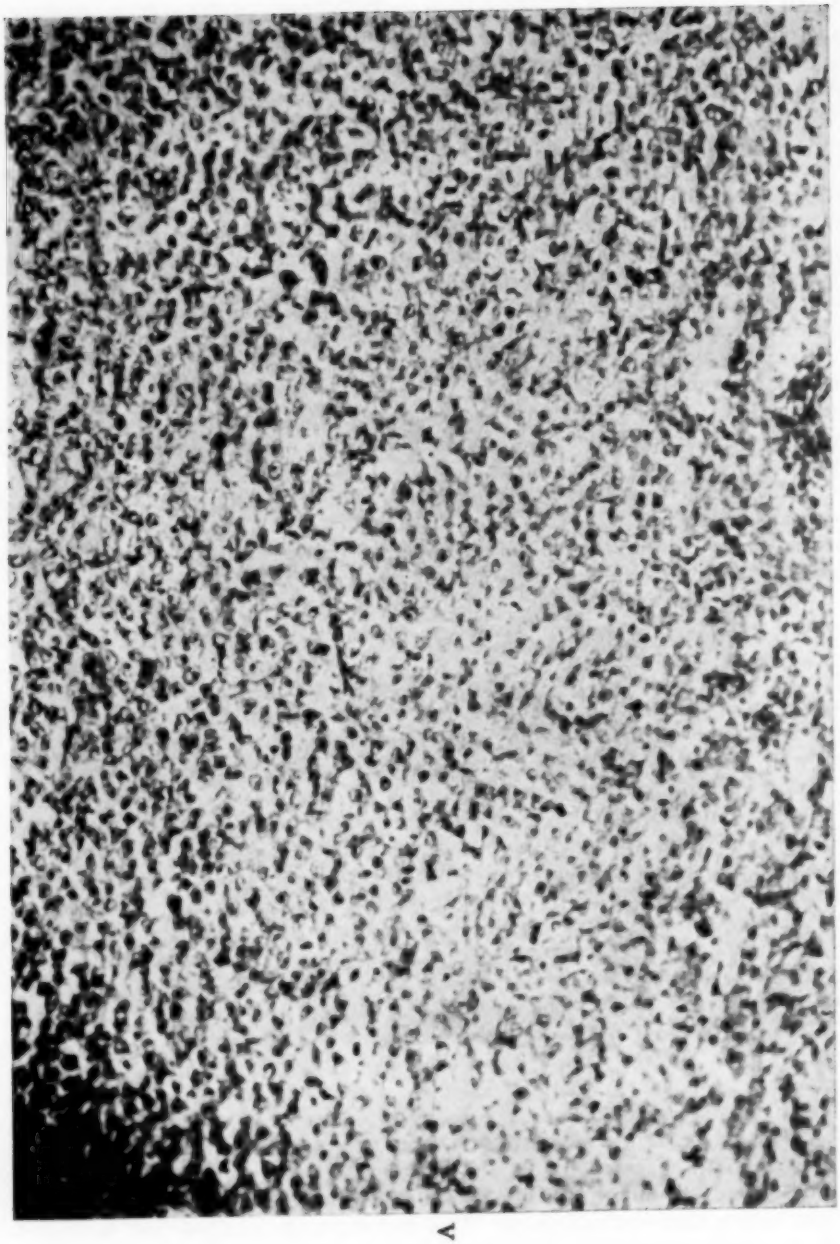
Pleural fluid was aspirated four times in 12 days, 1600 c.c. each time. It was turbid, not milky, but the specific gravity ranged from 1.017 to 1.021, the fluid contained much finely emulsified fat and had a high protein content. Pathological report of the fluid was "pleural exudate—no tumor cells."

Gastrointestinal examination revealed only chronic gastritis. An electrocardiographic tracing taken after the third pleural fluid aspiration showed sinus tachycardia, inverted T-waves in Leads I, II and III, but a normal Lead IV.

There was rapid reaccumulation of pleural fluid, later on both sides, and without other findings of cardiac failure. The fluid soon became creamy and remained so after April 23, 1940. Twenty-two aspirations were done up to September 10, 1940, with removal of a total of 42,900 c.c. of fluid. During this time there was progressive weight loss and emaciation. Because of the inconvenience and difficulty of returning to the hospital frequently, the patient was cared for at his home by the family physician after September 10, 1940. He died in December, 1940. There was no postmortem examination, but the family physician's clinical impression corresponded with that of our staff, namely, obstruction of the thoracic duct due to malignancy.

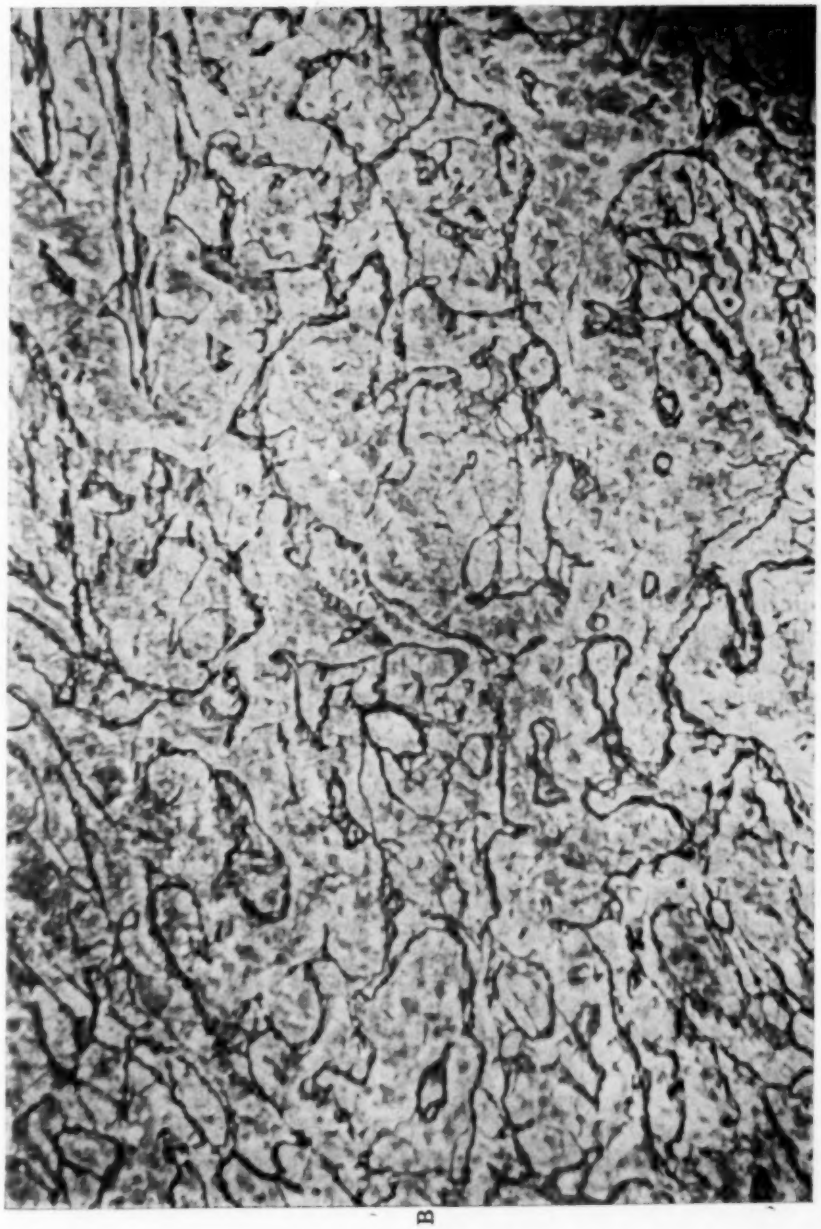
Case 3. F. C., a white woman, aged 63, was first seen at the hospital on December 20, 1941 because of pain in the right upper arm and shoulder of six months' duration. A lump had appeared on the left side of the neck in October, 1941, and, though painless, had steadily increased in size. Roentgenograms of the chest at that time had shown a mediastinal mass. This and the neck swelling had decreased in size with roentgen-ray therapy. Dyspnea followed and was relieved by aspiration of pleural fluid by the family physician.

Positive findings on admission to the hospital included: evident weight loss; pallor; weakness; several enlarged cervical lymph glands; flat percussion note over the lower half of the chest; and enlarged liver.



A

FIG. 2. Photomicrographs of section through cervical lymph node of case 2, showing complete destruction of architectural pattern. There are closely packed, large, irregular tumor cells with abundant cytoplasm and elongated branching processes. Nuclei are hyperchromic and contain numerous mitotic figures. A. Hematoxylin and eosin stain. B. Special reticulum stain.



B

branching processes. Nuclei are hyperchromic and contain numerous mitoses. ×
B. Special reticulum stain.

Roentgenograms of the chest showed suggestive widening of the mediastinum just below the clavicles, possibly due to glandular enlargement; fluid in both pleural cavities; and slight pneumothorax at the right apex.

Pathological report of biopsy of a cervical gland was "lymphoblastoma, reticulum-cell sarcoma type." A photomicrograph of this tissue is shown in figure 2.

Pleural fluid was milky, and, on standing, a creamy top layer formed. There was practically no odor. Specific gravity was 1.013. Fat was present in large quantity and could be easily seen microscopically. The protein content was 3.8 grams per 100 c.c. of fluid. Culture of the fluid was negative. It was unquestionably chylous fluid, reaccumulating rapidly and showing the same characteristics each time that it was aspirated. A total of 6500 c.c. was removed in five aspirations.

The patient responded very poorly to roentgen-ray and symptomatic therapy, became progressively weaker and more emaciated, and died February 5, 1942.

The autopsy report is as follows: "Lymphoblastoma, reticulum-cell sarcoma type, involving the entire lymphoid system, epicardium, liver, lungs, pleura, kidneys and pericardial tissues; early lobar pneumonia; pulmonary fibrosis; fibrinous pleuritis; bilateral chylothorax; aortic atherosclerosis; mild arteriosclerotic disease of kidneys."

Comment

The appearance of chylous fluid in one or the other pleural cavity seems to bear some relation to the location of the perforation in or obstruction to the thoracic duct in its anatomical course. The latter has been ably reviewed by Gordon [8] and Brescia,[1] and will not be discussed here. However, it would seem that injuries or obstruction to the duct lower down would account for effusion presenting itself on the right side, whereas those higher up would produce effusion on the left. Because of anomalies of the duct or extensive involvement as from trauma or new growth, there are exceptions, as illustrated by Heppner's case.[21]

Etiology

Chylous fluid in the pleural cavity results from any condition that interferes with the normal flow of chyle through the thoracic duct, either from a break in the duct or obstruction to it. Revising and enlarging upon the causes given by McNabb and Scarlett,[22] I would summarize the etiological factors as follows:

I. Destructive damage to the thoracic duct or its terminals.
   1. Trauma to the chest without fracture of bone.
   2. Trauma to the chest with fractured ribs, clavicle or vertebrae.
   3. Duct accidentally severed at operation.
   4. One or more terminals severed.
   5. Gunshot or stab wounds.
   6. Perforating lymphangitis involving duct or terminals.
   7. Aneurysm of duct with rupture.

II. Obstruction to the thoracic duct.
   1. Within the duct or terminals.
      a. New growth.
      b. Filaria.

2. From outside the duct.
   a. New growths and granulomata; carcinoma, lymphosarcoma, tuberculous glands.
   b. Thrombosis of left subclavian vein.
   c. Cirrhosis of liver.

III. Spontaneous or of unknown origin.

The spontaneous type occurs in infants under one year of age in whom a congenital defect or weakness of the duct must be strongly considered. In seven of 10 infants under one year of age reviewed by Brescia,[1] the cause for chylothorax was given as spontaneous.

Trauma is by far the largest single cause. Though Shackelford and Fisher [23] succeeded in tracing only 41 authentic traumatic cases to which they added two of their own in 1938, Høyer [5] in the same year reported 48 out of a total of 84 from all causes, and, of the eleven other reported cases we have added, eight were traumatic.

Various types of trauma are described. Crushing injuries to the chest are the most common according to Shackelford and Fisher.[23] One of the earliest cases due to chest injury was reported by Finkelstein [24] in 1901. Final rupture of the duct occurred with a severe cough that developed after a latent period of a month. Another with a still longer latent interval was reported by Beatty,[25] actual symptoms of chylothorax developing six and one half years after an automobile accident. Straus [26] describes a case due to a bullet wound of the thoracic duct, one of the rarer traumatic causes.

Two of the cases reported in this paper were due to new growth outside the thoracic duct and the third was thought due to malignancy also, though this was not established by actual pathological diagnosis or by autopsy. In adults, this, namely malignancy, is the second most common cause of chylothorax.

Diagnosis

This is dependent on thoracentesis and careful examination of the fluid. The chief characteristics of chylous fluid according to Gaudin,[27] Nowak and Barton,[4] and Wallis and Scholberg [28] are the following:

1. Milky appearance.
2. Generally shows distinct creamy layer on standing.
3. Finely emulsified, with fine fat globules.
4. No odor or odor corresponding to odor of food eaten.
5. Reaction alkaline.
6. Specific gravity generally exceeds 1.012.
7. Degree of opalescence more or less constant.
8. Sterile and resists putrefaction.
9. Fat content generally high, 0.4 to 4 per cent, and like fat in food.
10. Total solids usually greater than 4 per cent.
11. Total protein generally exceeds 3 grams per 100 c.c.
12. Salts and organic substances approximate the values found for chyle from the thoracic duct.

The fluid may also be examined microscopically for fat droplets. In traumatic cases, Lillie and Fox [29] mention as aids in diagnosis such striking clinical features as:

1. The latent period before onset of symptoms (it takes time for the fluid to penetrate the pleural wall).
2. Rapid reaccumulation of fluid within the chest after aspiration.
3. The gradual progressive emaciation which frequently ends in death.

In addition to the features mentioned, Mouchet [30] observed:

1. Collapse or shock, caused by change in intrathoracic pressure.
2. Inanition, oliguria, and thirst, probably from breakdown of lipid metabolism or loss of some unknown hormone or enzyme.

Prognosis

The outlook in most of these cases is usually grave. The reported mortality in traumatic chylothorax is approximately 50 per cent, in spite of various methods of therapy, and in the cases due to new growth, the outcome is invariably fatal. The loss of fluid so rich in protein and fat as chyle quickly leads to dehydration and malnutrition if not replaced by various forms of therapy.

Treatment

Smith and Woliver [13] feel that the therapy of chylothorax must satisfy several requirements, namely prevention of the loss of chyle, maintenance of nutrition and prevention of infection in the chest. This means essentially, then, aspiration and, if possible, intravenous reinfusion of the aspirated fluid, as was attempted by Oeken [31] and later done by Bauersfeld.[32] The fluid aspirated may be stored in the ice box and then given intravenously as desired, first being sure it is sterile by culture. Aspirations should be done only as necessary to relieve respiratory distress, since the increased pressure of fluid may help to close a fistula. Some writers recommended a low fat diet to decrease the flow of chyle.

Smith and Woliver [13] feel that early operation for traumatized ducts is not advisable because of the usual inaccessibility of the duct or the poor condition of the patient. Besides, these tears often heal or close spontaneously. These authors feel that open external drainage of chyle should be avoided unless empyema supervenes. Yet, most writers are agreed that surgery has a place, such as correction of deformity from fracture of a clavicle causing pressure, or suture of a ruptured duct in the supraclavicular portion. Nowak and Barton [4] cured their case by phrenicotomy, the stoma apparently being walled off by the resultant elevation of the diaphragm. They suggest phrenicotomy or phrenic nerve crushing if repeated aspiration and intravenous reinfusion fail to produce adequate response. And Brown [33] feels that in those cases with a rather long latent period and an early stage of effusion, termed "retropleural chyloma," early thoracotomy and extrapleural drainage should be done with the object of preventing rupture or diffusion into the pleural space. Selection of cases for surgery is important.

Summary

1. The relative rarity of chylothorax is emphasized by the fact that up to the time of this report only 102 cases could be collected from the literature. There are probably others not recognized or reported.

2. Traumatic cases predominate but those due to new growths outside the thoracic duct are not uncommon. Two of the cases here reported and probably the third were due to new growth outside the duct.

3. Diagnosis is dependent primarily on aspiration and identification of chylous fluid.

4. Treatment consists essentially of aspiration of fluid as necessary to relieve respiratory distress, and intravenous reinfusion of the fluid to prevent rapid emaciation. In selected cases surgery is advisable. With any treatment, however, the prognosis is invariably poor.

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CHORDOMATA: A REVIEW OF THE LITERATURE, WITH REPORT OF A SACROCOCCYGEAL CASE *

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INTRODUCTION

CHORDOMATA are tumors that arise from remnants of the fetal notochord. These remnants may be situated in any of the intervertebral discs and in the region of the spheno-occipital or sacro-coccygeal articulations. They rarely occur in the mandible or maxilla. These notochordal remnants frequently give rise to small tumors termed ecchordosis physaliphora by Luschka [1] in 1856, and by Virchow [2] in 1857. Virchow considered these tumors to be of cartilaginous origin, but Ribbert,[3] supported by Müller's [4] theory, believed that they arose from remnants of notochordal tissue. Ribbert noted the resemblance of the cells to those of the notochord, and furthermore produced experimental evidence to support his view. Remnants of notochordal tissue persist in the nucleus pulposus of the intervertebral discs of vertebrates. Ribbert punctured the intervertebral disc of a rabbit allowing the nucleus pulposus to extrude. A tumor resembling chordoma developed at the site of the injury.

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Embryology

The notochord develops from the entoderm, and in the embryo lies as a solid cord extending lengthwise of the body, ventral to the neural canal. As the embryo develops, mesodermal tissue surrounds the notochord and from this mesodermal tissue the vertebrae and intervertebral discs develop. The notochord thus is embedded in the bodies of the vertebrae and in the intervertebral discs. The vertebral portion disappears, but in the discs notochordal tissue persists as the nucleus pulposus. In its earliest stages, the notochord is first a hollow tube, and then a solid cord of non-vacuolated, polygonal, undifferentiated epithelial cells surrounded by a hyaline-like sheath. Later, the cells become vacuolated. These vacuoles contain a gelatinous, mucin-like substance which later escapes from the cell, forming a mucinous matrix in which lie syncytial-like groups of cells.

Bruce and Mekie [5] consider that chordomata resembling the early stages of the developing notochord are most malignant and those resembling the later stages, least malignant. Bérard, Dunet, and Peyron,[6] and Linck and Warstadt,[7] in a study of human embryos, demonstrated notochordal tissue lying on the surface of the vertebral bodies chiefly in the lumbosacral area. These portions of the notochordal tissue on the surface of the vertebral column were connected with the notochord itself by thin strands of notochordal tissue. Chordomata probably arise from these misplaced notochordal tissues. Another possibility is that they arise from the nucleus pulposus with injury as a contributing factor, in a few instances. A history of antecedent trauma was noted in 14 cases by Peyron and Melissinos [8] in 1935. In the cranial region, nodules of notochordal tissue are found lying on the Clivus Blumenbachii in about 2 per cent of autopsies. Tumors may develop from these nodules, and project into the cranial cavity, in the sphenoidal sinus, or into the pharynx.

Bruce and Mekie [5] stated "that once encased in bone, the notochordal tissue does not usually survive, but in the absence of a bony envelope it may, and often does, persist. In the situations where normal persistences have been shown to be likely, there is the further feature that the notochordal tissue is not even restrained by a sheath of fibrous tissue as in the case of the nucleus pulposus of the discs."

Histology

In 1922, Alexais and Peyron [9] presented a comprehensive study on the histogenesis and origin of chordomata. Their report was based upon the examination of nine tumors. They stated that vacuolization of the cellular elements affecting the cytoplasm and intercellular spaces about the ectoplasm was a specific characteristic of chordal tissue. They also stated that the vacuoles contained a substance of a mucin-like character. The cells may be arranged in groups, about cavities, and appear prismatic or cuboidal in shape. There may be plain cellular strips of epithelial type with dense cytoplasm filled with vacuoles, interspaced regularly with vascular endothelium. There may be cellular elements of a fusiform or polymorphous type, analogous to those of sarcomata. Lastly, there may be a network of fibrils of a remarkable fineness, appearing in the vacuolized zones, coincident with a syncytial evolution which makes the cellular limits disappear almost completely.

The stage of non-vacuolated polygonal cells is said to be the most malignant type of chordoma. The stage of vacuolated mucin-containing cells is of moderate malignancy. The syncytial stage of intercellular mucoid degeneration is said to be the most benign type of chordoma. Fletcher, Woltman, and Adson,[10] in 1935, summarized the histopathologic characteristics of chordomata as follows: "(1) the formation of intracellular and extracellular mucus; (2) the presence of physaliphorous or huge vacuolated mucus-containing cells; (3) the lobular arrangement of the tumor cells, which usually grow in cords; (4) the occasional occurrence of vacuolation of the nuclei; and (5) the close resemblance to notochordal tissue as seen in the nuclei pulposi of the intervertebral discs."

Historical

In 1925, Coenen[11] gave the following classification of chordomata: (1) cranial, including the clivus chordoma (both benign and malignant), the hypophyseal, and the nasopharyngeal chordomata; (2) vertebral chordomata; and, (3) caudal or sacrococcygeal chordomata, including the antesacral, retrosacral, and central forms. This classification is still used.

Remnants of notochordal tissue were first found by Klebs,[12] in 1864, in the spheno-occipital region. In 1903, Grahl[13] reported the first case of spheno-occipital chordoma. Trélat,[14] in 1868, reported a case of chondroma of the neck, which at operation was found attached to the cervical vertebrae. This case was thought by DesJacques[15] and again by Owen, Hershey, and Gurdjian,[16] in 1932, to have been a chordoma. The case reported by Raul and Diss,[17] in 1924, was the first authentic case of vertebral chordoma in which the tumor was located in the cervical region. In 1900, Hennig[18] reported the first case of sacrococcygeal chordoma. Since then many cases in both the spheno-occipital and sacrococcygeal regions, and a few vertebral cases have also been reported.

Résumé of Cases

There have been several comprehensive reviews of the reported cases in the past. The first of these was in 1922 by Stewart,[19] followed by Eckel and Jacobs[20] in 1925, and Coenen[11] again in 1925. In 1926, Stewart and Morin[21] reported a total of 55 cases distributed as follows: (1) region of spheno-occipital synchondrosis—25, (*a*) projecting into the cranium—16; (*b*) projecting into the nasopharynx only—1; (*c*) projecting in both directions—8; (2) occipital region—1; (3) upper and lower jaw—1; (4) sacrococcygeal region—27, (*a*) projecting anteriorly—12; (*b*) projecting posteriorly—8; (*c*) projecting in both directions—7. They found that approximately 70 per cent occurred in males, and that the average age incidence was 34.9 years for the spheno-occipital chordomata, and 50.6 years for the sacrococcygeal region, with a variation from 16 to 72 years. The limits of duration in the cases they studied were from two to eight years. Since then, cases have been reported in infants and very young children by Montgomery and Wolman[22] in 1933.

In 1930, Machulko-Horbatzewitsch, and Rochlin[23] reviewed a series of 103 reported cases, and found 49 cranial cases, eight vertebral cases, and 46 caudal cases. In 1935, Mabrey[24] reviewed 150 cases, and found 49 were in the cranial region, seven in the cervical, two thoracic, five lumbar, and 87 sacrococcygeal.

Of this series there were 27 autopsies in the cranial group, 10 of which showed metastases, giving an incidence of 62.55 per cent. In 1933, Montgomery and Wolman [22] reported three cases of chordoma present at birth, of which one was sacrococcygeal and two were intracranial. They also reported four cases of sacrococcygeal chordomata occurring in infant girls, all of which were inoperable, one with hepatic, and one with pulmonary metastases.

TABLE I

Spheno-Occipital Chordomata Reported since 1935

Year	Author	No. of Cases
1927	Ajello[25]	1
1931	Klotz[26]	1
1933	Kling[27]	1
1934	Traina[28]	1
1934	Haas[29]	1
1934	Camauer and Sacon[30]	1
1934	Harbitz[31]	1
1935	Livingston[32]	1
1935	Furlow[33]	1
1935	Adson et al.[34]	2
1935	Van Wagenen[35]	2
1935	Fidlovosky[36]	1
1936	Cusenza[37]	1
1936	Stevenson and Freidman[38]	2
1936	Gould[39]	1
1936	Boemke and Joest[40]	2
1936	Gutierrez and Monserrat[41]	1
1937	Argaud et al.[42]	1
1937	Braitenberg[43]	3
1937	Dickson et al.[44]	1
1937	Hrynkiewicz[45]	1
1937	Roche and Martin[46]	1
1937	Szeker[47]	1
1938	Peers[48]	1
1938	Ridpath[49]	2
1938	Schneegans and Mandigas[50]	1
1938	Calamandrai[51]	1
1938	Remaggi[52]	1
1939	Zambrini and Castellanos[53]	1
1939	Moller[54]	1
1941	Zeitlin and Levinson[55]	1
1941	Boldrey and McNally[56]	4
1941	Gardner and Turner[57]	3
	Total since 1935	45
	Total reported by Mabrey	47
	TOTAL	92

TABLE II

Sacrococcygeal Chordomata Reported since 1935

Year	Author	No. of Cases
1926	Karsner (from Stewart)[19]	1
1933	Grandclaude et al.[58]	1
1935	Pupo and Tarafa[59]	1
1935	Fletcher et al.[60]	7
1935	Roche et al.[61]	1
1936	Schwartz et al.[62]	1
1936	Harmos and Palmer[63]	1
1936	Hsieh and Hsieh[64]	1
1936	Gabriel[65]	1
1936	Simonds[66]	2
1937	Cazzamali[67]	1
1937	Schwyzer[68]	1
1937	Nash and Laskey[69]	1
1937	Barnes and Owen[70]	1
1937	Coley[71]	1
1937	Bruce and Mekie[5]	2
1937	Braitenberg[43]	2
1938	Ghareeb[72]	2
1938	Ruckensteimer[73]	1
1938	Bobbio[74]	1
1938	Nagase[75]	1
1939	Ashour[76]	1
1939	Lyall[77]	1
1940	Mixter and Mixter[78]	1
1940	Bowers[79]	1
	Total since 1935	35
	Total reported by Mabrey	87
	TOTAL	122

TABLE III

Vertebral and Other Chordomata Reported since 1935

Year	Author	No. of Cases
	Vertebral	
1868	Trélat[14]	1
1887	Hermann and Tourneaux[80]	1
1889	Klebs[81]	1
1926	Andler[82]	1
1928	Dowling and Sepich[83]	1
1929	Hutton and Young[84]	1
1929	Hermann[85]	1
1930	Rocher and Guerin[86]	1
1934	Harbitz[87]	1
1935	Fletcher et al.[10]	1
1935	Ellis[88]	1
1935	Adson et al[34]	1
1936	Ohein[89]	1
1936	Albert[90]	1
1937	Cabot[91]	1
1938	Bertoni and Fratini[92]	1
1939	Güthert[93]	1
1940	Mixter and Mixter[78]	2
1940	Richards and King[94]	1
	Total since 1935	20
	Total reported by Mabrey	14
	TOTAL	34
	Others	
1934	Landivar (jaw)[95]	1
1939	Ashour[76] (ant. larynx)	1
	Total since 1935	2
	Total reported by Mabrey	2
	TOTAL	4

We have reviewed the literature and those cases not included in Mabrey's list, and those that have been reported since 1935 are included (tables 1, 2, and 3). The number of cases found in each location is as follows: (1) cranial (including spheno-occipital and nasopharyngeal cases)—92; (2) vertebral—34; (3) caudal (or sacrococcygeal)—122; (4) others—4. Thus it will be seen that 48.4 per cent of the reported cases are found in the sacrococcygeal region, and 36.5 per cent in the cranial region, the remainder being located along the vertebral column, with few exceptions.

SYMPTOMATOLOGY

The signs and symptoms of the cranial chordomata are those of a brain tumor, or a tumor of the nasopharyngeal cavity, with headache and diplopia, or difficult nasal breathing among the most common symptoms, as the case may be. Nausea, vomiting, and vertigo are also frequently found. Involvement of one or several of the cranial nerves from the pressure of the growth almost always occurs, with consequent pupillary changes, disturbances of the senses of smell, vision, and occasionally hearing and speech. There may be strabismus, hemianopsia, optic atrophy, papilledema, nystagmus, dilatation of the pupil, and loss of light and consensual reflexes, depending upon the cranial nerves involved in the new growth. The involvement is most frequently unilateral, but occasional bilateral involvement has been noted. Hemiplegia, paraplegia, incontinence of urine and feces, and peripheral muscle weaknesses have been reported. Loss of weight and general weakness occur infrequently. In those cases in which the growth is predominantly anterior, difficult breathing results from the protrusion of the growth into the nasopharynx, and occasionally the posterior segment of

the nose. Epistaxis occasionally occurs in such cases. The mass may be seen or palpated in the nasopharynx when the latter is involved. Roentgenograms may or may not show signs of increased intracranial pressure, with erosion or destruction of the bones in the region of the spheno-occipital articulation or the sella turcica.

The signs and symptoms of chordomata of the spine are those of pressure, due to the increasing size of the tumor mass. The growth may progress anteriorly or posteriorly, as in other regions, or remain centrally located. It frequently causes erosion of the adjacent vertebrae. In the upper cervical region the growth may protrude into the pharynx, with consequent difficulty in swallowing or respiration. In the lower cervical region, the progress of growth may be into the lateral or posterior neck muscles, the mass being visible externally, and causing painful and difficult neck movements. Coincident with these symptoms, those due to pressure on the brachial plexus and the spinal cord arise, with various paralyses and paresthesias or anesthetic areas, either in one or both of the upper extremities. When the tumor mass encroaches on the cord, whether in the cervical, dorsal, or lumbar region, the signs are those of a spinal cord tumor, with sphincter paralyses, either unilateral or bilateral paralyses of the muscles below the level of the tumor, and the development of areas of hypoesthesia, or anesthesia. The deep reflexes of the involved areas may be either increased or decreased. Ankle clonus may develop.

In the dorsal region, the growth is most commonly into the mediastinum, with pressure on the aorta or the esophagus, resulting in pain in the chest, frequently substernal, and difficulty in swallowing. There may be more or less complete obstruction of the esophagus. In the lumbar region, pressure on abdominal organs may cause symptoms referable to these organs, in addition to those symptoms noted above.

As in cranial and vertebral chordomata, the signs and symptoms of sacrococcygeal chordomata are those due to the pressure of the gradually increasing tumor mass and its encroachment on structures in the pelvis. The tumor most frequently grows anteriorly and is palpable as a firm mass in the rectal pouch on digital examination, or seen on proctoscopic examination to be obstructing the rectum or constricting its lumen, and digital examination may show the mass more or less completely filling the pelvic cavity if it is in an advanced stage. In large growths in this region, the ureters may be displaced and the bladder pressed upon. Consequently, there may be difficulty in defecation and occasionally in micturition. The feces may be blood stained, or there may be frank hemorrhage from the rectum. The tumor may extend posteriorly, and if so, appears as a mass of variable size, occasionally of tremendous size, over the sacrum or nates. Growth may progress both posteriorly and anteriorly, or into the abdomen, as in the case we are reporting. Paralyses, hypoesthesias, or anesthetic areas of one or both the lower extremities develop as a result of the pressure of the tumor mass. Pain over the mass, in the rectum, and radiating over the course of the involved nerves is frequent. Difficulty in walking may be an early symptom.

The roentgenographic signs of sacrococcygeal chordomata were stated in 1936 by Hsieh and Hsieh [64] as: "1. *Expansion.* This may be demonstrated in the antero-posterior or lateral views, preferably by stereoscopic examination of

the bone which may or may not be entirely preserved. 2. *Rarefaction or Destruction.* The involved bone presents either a loculated appearance with multiple small circular or oval radiotranslucent areas or the bone is destroyed in large areas. 3. *Trabeculation.* The remains of the undestroyed bone form dense trabeculae which may extend into the soft tissue mass outside the original normal boundary of the bone. 4. *Calcification.* This may be due to reactive new bone formation or deposit of calcified material in the tumor as a result of degeneration or necrosis. This calcified matter appears usually in irregular masses of soft radio-opacity." They stated that these "findings elsewhere in the skeleton may indicate giant-cell tumor, osteochondroma, or myxochondroma, but the clinical picture and particularly the sacrococcygeal location of the lesion should suggest the diagnosis of chordoma."

Similar roentgenographic findings may be noted when the tumor is located in the vertebral column or in the cranium, if the tumor has been one of comparatively long standing, but these findings are not at all of a positive diagnostic nature. Roentgenograms are frequently entirely normal even in well advanced cases.

Encephalograms and myelograms may be of distinct aid in localizing or discovering the presence of a cranial or spinal chordoma, but the proof that the lesion is a chordoma must wait an examination of the tissue microscopically.

Differential Diagnosis

The nature of the tumor when found cannot be definitely stated without microscopic examination of the tissue, but it can be continually borne in mind in considering the types of tumors that are located in the spheno-occipital or the sacrococcygeal region, and should not be forgotten in tumors of the vertebral column. A histopathological diagnosis is at times most difficult as there may be elements in the tissue which would strongly resemble those found in myxochondroma or sarcoma, or gelatinous carcinoma of the rectum. If the tumor mass surrounds the rectum a gelatinous carcinoma of the rectum may be strongly considered, but a chordoma is more firmly attached to the sacrum by strands of attachment than is a carcinoma. The histologic features of chordomata have been discussed in detail above. Teratomata, dermoid cysts, enchondromata, osseous sarcomata, myelomata, tuberculosis of the sacrum, and carcinomata of the rectum must all be differentiated from sacrococcygeal chordomata. Diagnostic puncture of the tumor mass, when accessible, is of aid in establishing a diagnosis.

Ridpath [49] stated in 1938 that there are "many good reasons for confusing chordoma with craniopharyngioma (a tumor of Rathke's cleft and hypophyseal stalk). The manifestations referable to the cranial nerves, especially defects in the visual fields, and the roentgenographic changes may be identical. There may even be suprasellar calcification, such as is common in a craniopharyngioma. The adenomata and carcinomata of the hypophysis may destroy a considerable amount of bone, and in order to complete the imitation of a chordoma, they may grow into the nasopharynx." In spheno-occipital chordomata "there is little or no evidence of hypophyseal dysfunction." He stated that among the other tumors to be differentiated are parasellar meningiomata, atypical chondro-

mata, chondrosarcomata, myxosarcomata, pharyngeal dermoid cysts, teratomata, and primary nasopharyngeal carcinomata.

Prognosis

Benign and malignant chordomata are both notably rather slow in growth. In the former, the process may cover a period of many months or several years before the symptoms are pronounced enough for the patient to seek relief. In the latter, the progress of growth is likewise variable, but is usually much more rapidly progressive than in the benign type. However, several years may elapse in malignant cases that show definite metastatic lesions at the time of the first examination. As a rule, the cranial type is the most rapidly fatal. Benign growths if not completely removed at operation continue to grow. Metastases in the malignant type occur in the minority of cases, and are found in the adjacent lymph nodes, heart, lungs, liver, spleen, kidneys, and adrenals. The adjacent tissues are frequently involved by direct extension of the growth.

Treatment

In areas that are accessible to surgical removal of the tumor, operation offers the only hope of a permanent cure. If completely removable, recurrence does not occur in the benign type, and complete recovery ensues. Because of the location, size and extent of the growth, and involvement of adjacent structures, complete removal and consequent cure are not often possible. Relief of untoward pressure symptoms with partial removal, however, is indicated whenever possible, even if this requires repeated operations as symptoms recur. Malignant chordomata are, of course, always fatal, unless successfully and completely removed before metastases occur. Surgical removal is often a most difficult and arduous procedure, and in cases in which extensive areas of bone are involved, an impossible task. Roentgen and radium therapy have both been used following operation, and without operation, but with very questionable results. Some relief of pain may result, but little can be expected as far as retarding or curing the tumor when this method of treatment is employed.

Case Report

H. J. J., colored male, aged 23 years, was admitted to Walter Reed General Hospital, Washington, D. C., on March 24, 1938. His chief complaints were intermittent dull pain in the right lumbar region, loss of weight and strength, a rather harassing productive cough, dyspnea on exertion, anorexia and constipation. His past and family history were irrelevant except that he had had influenza in 1933, and gonorrhea in 1931. The present illness started in the summer of 1937, with a severe nasopharyngitis and bronchitis. His health had declined from then on, the cough becoming chronic and productive of a yellow-grayish material, occasionally streaked with blood. There was a sense of tightness in the chest. During the first part of 1938, the condition became worse, strength failed, and he developed a tendency to perspire, had dyspnea on exertion, constipation, and intermittent dull pain in the right lumbar region.

Physical examination on admission showed a young colored man, underweight and obviously chronically ill. The temperature was 98.8° F., pulse 112, respirations 32. His normal weight had been 135 pounds, and was 114 pounds on admission. The inguinal

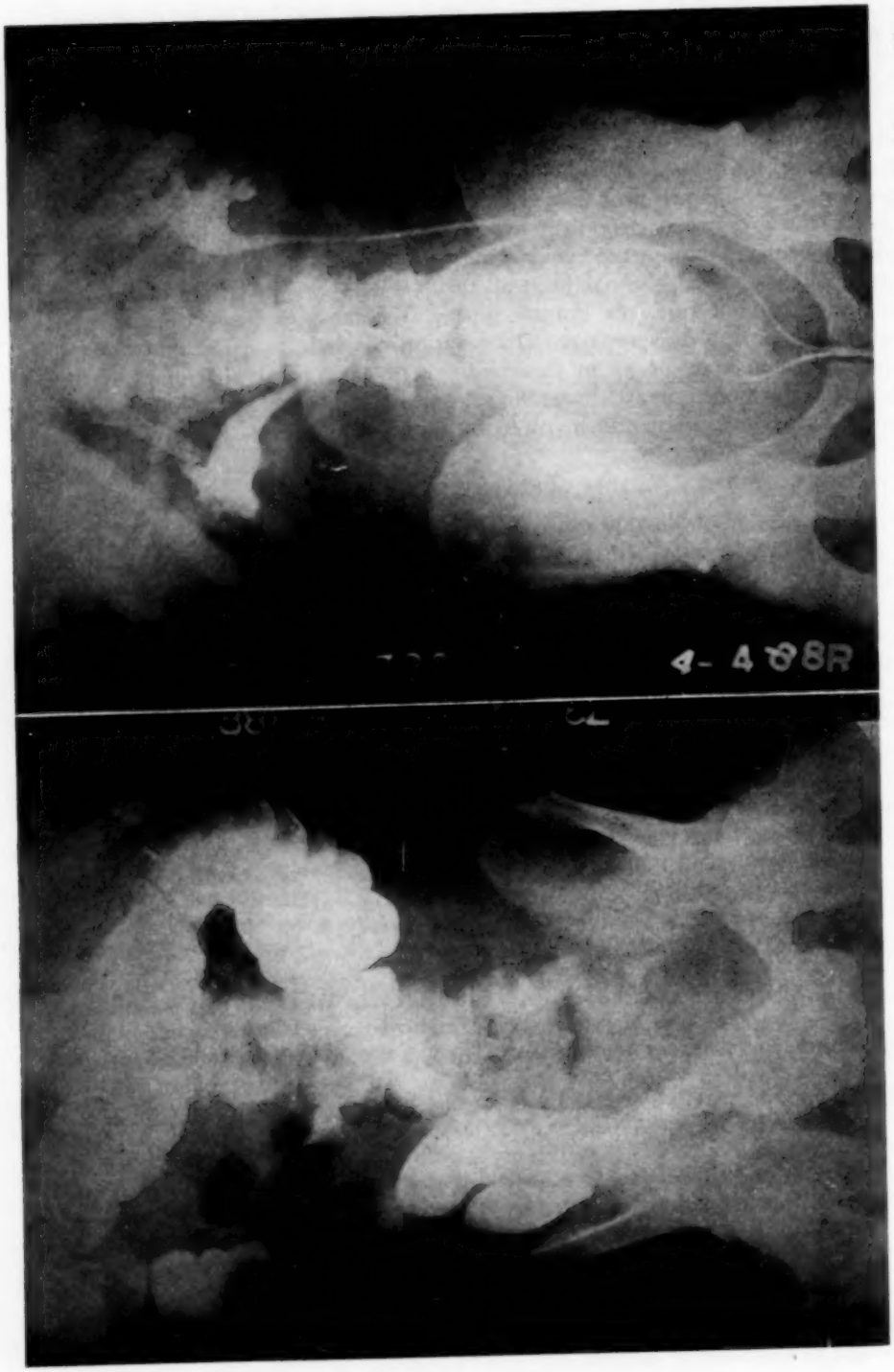

FIG. 1. (Left) Barium enema showing displacement of the descending colon to the left. (U. S. Army, Medical Museum Neg. No. 68292, Acc. No. 62185.)
FIG. 2. (Right) Urogram showing marked displacement of ureter to the left. (U. S. Army Medical Museum Neg. No. 68293, Acc. No. 62185.)

glands were enlarged and firm, and there was a generalized enlargement of all the lymph glands. The tonsils were moderately enlarged. The blood pressure was 124 mm. Hg systolic and 64 mm. diastolic. The heart rate was accelerated, but the heart was otherwise normal. Examination of the lungs showed impaired resonance bilaterally, ranging from dullness to flatness at the posterior right base. There were moist, crackling râles, in the left lower lobe posteriorly and in the axilla. There were diminished breath sounds with prolongation of expiration in the lower right lung. Tactile fremitus was absent in the right base posteriorly. The prostate was soft and somewhat tender. The abdomen was flat, with the liver edge barely palpable. There was a firm fixed mass in the right lower quadrant, extending into the right flank, tender to pressure, appearing attached to the pelvis. The pupils were normal, as were the pupillary reflexes. The knee jerk on the right was absent. Other reflexes were normal.

The blood count on admission was 4,160,000 red cells, hemoglobin 70 per cent, 12,000 white cells, with 72 per cent neutrophiles, 19 per cent lymphocytes, 7 per cent monocytes, and 2 per cent eosinophiles. The Wassermann test showed a two plus reaction on two occasions, with the Kahn test four plus on one occasion, and two plus on the second. The blood chemistry was within normal limits. Urinalyses were negative, including cultures. The sputum was negative for tubercle bacilli on repeated examinations. The feces were negative for parasites and ova, free and occult blood. The fractional gastric analysis showed a low total acid curve, with absence of free hydrochloric acid in all but one specimen. A barium enema showed the colon and cecum displaced to the left (figure 1). A flat film of the kidney, ureter and bladder regions showed a faint outline of the mass in the right side of the pelvis. A urogram gave the impression of a tumor mass in the abdomen, in the right lower quadrant, in relation to the right kidney (figure 2). Gastrointestinal studies were negative. Metastatic growths were noted throughout both lungs on roentgenograms taken on admission (figure 3), and these increased in size throughout the period of hospitalization. No metastases were evident in roentgenograms of the lumbar vertebrae, bones of the pelvis, femora, or the skull.

Soon after admission a lymph gland from the right inguinal region was removed and showed on microscopic examination a low grade, chronic, non-suppurative inflammatory reaction. As it was not feasible to make any further attempts at a positive diagnosis, because of the far-advanced nature of the tumor, a working diagnosis of an unknown variety of malignant tumor of the right lower abdomen was made. The possibility of the origin of the tumor at the lower pole of the right kidney was considered. On April 3, 1938, he had a rather severe pain in the right lower extremity, and this recurred at varying intervals and with varying intensity throughout his period of hospitalization. Deep roentgen therapy was started on April 7, 1938, and completed on May 6, 1938. A total of 4,100 r. to six chest fields, and 4,100 r. to three abdominal fields was given, with only slight diminution in the size of the abdominal mass. In June 1938, codeine was required to control the troublesome nocturnal cough, and for the pain in the right lower extremity. In December 1938, deep roentgen therapy was again given, starting on December 1, 1938, and completing the course on January 19, 1939. A total of 1,784 r. was given to the abdominal fields.

During the course of treatment in the hospital a rather severe secondary anemia developed with the red cell count dropping to 2,300,000 and hemoglobin to 50 per cent. The white cell count varied from 3,450 to 18,400, but it was usually within normal limits. Eosinophiles were present on repeated blood counts, and at times were as high as 20 per cent.

The patient remained up and about until the middle of January 1939, when he became much worse, with more pain in the right hip joint, radiating down the right lower extremity, and with considerable aggravation of the productive cough. The

FIG. 1. (Left) Barium enema showing displacement of the descending colon to the left. (U. S. Army Medical Museum Neg. No. 68293, Acc. No. 68292, Acc. No. 62185.)
FIG. 2. (Right) Urogram showing marked displacement of ureter to the left. (U. S. Army Medical Museum Neg. No. 68293, Acc. No. 62185.)

mass in the right lower abdomen had become larger. Morphine was required occasionally to control the pain. By the middle of February 1939, morphine was required four to five times in 24 hours for relief of pain, and cough. The right lower extremity had become mildly edematous. By the middle of March there was moderate edema of both legs and ankles, but he was still able to get out of bed for short periods.

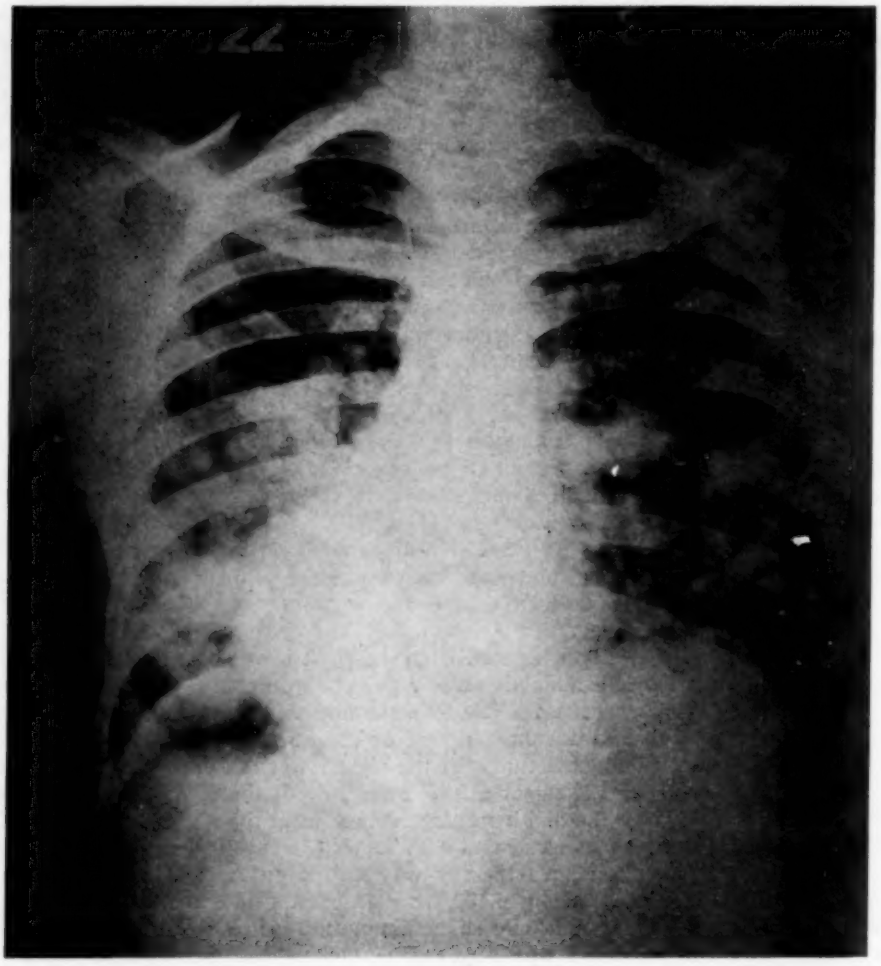

FIG. 3. Roentgenogram of the chest on admission showing metastatic growths throughout both lungs. (U. S. Army Medical Museum Neg. No. 68294, Acc. No. 62185.)

He died quietly on March 21, 1939, at 8:15 a.m. The antemortem diagnosis was retroperitoneal tumor of unknown type, with metastases to the lungs.

Autopsy. Gross findings: The skin showed scattered, superficial ulcers, 1 cm. to 2.5 cm. in diameter in the following areas: right mastoid, left ear, face, thorax, abdomen, and back. The right leg and ankle showed moderate edema and the left leg and ankle slight edema.

In the right lower quadrant of the abdomen was a firm, smooth, immovable globular mass which was easily visible projecting above the surface of the abdomen. It measured 15 by 8 cm. The skin was not adherent to the mass.

FIG. 4. (Right) Anterior and posterior views of tumor mass removed from right lower abdomen. (U. S. Army Medical Museum Neg. No. 68287, Acc. No. 62185.)
FIG. 5. (Left) Gross section of tumor showing lobulated surface with areas separated by fibrous septa. (U. S. Army Medical Museum Neg. No. 68289, Acc. No. 62185.)

The right pleural chink contained 500 c.c. and the left pleural chink 100 c.c. of clear, straw-colored fluid. The lungs were free, the right weighing 1,320 grams, and the left 1,020 grams. Both the pleural and cut surfaces of the lung were studded with grayish-white, fairly firm tumor nodules varying in their greatest diameter from

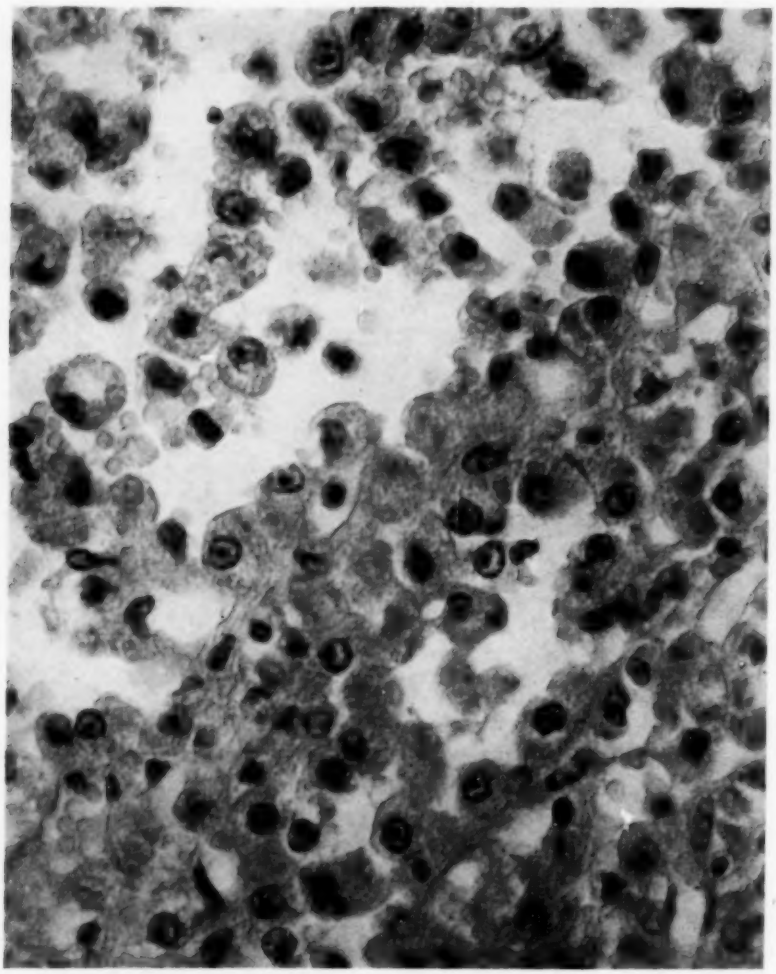

FIG. 6. Large cells with prominent nuclei with occasional vacuoles. (U. S. Army Medical Museum Neg. No. 68666, Acc. No. 60677 × 575.)

0.5 cm. to 4 cm. These nodules were well circumscribed and were distributed throughout all lobes of both lungs. They did not encroach upon bronchi and did not involve the parietal pleura. Mediastinal nodes showed no evidence of tumor.

The cardiovascular system showed no abnormalities.

The peritoneal chink contained about 500 c.c. of clear straw-colored fluid.

The gastrointestinal tract and the mesenteric and retroperitoneal nodes were normal.

FIG. 7. Collection of chordoma cells within the lumen of a small capillary. (U. S. Army Medical Museum Neg. No. 68668, Acc. No. 60677 × 575.)

No gross lesions were found in the liver, spleen, pancreas, kidneys, bladder, prostate, thyroid or thymus. Sectioning of the left adrenal showed a grayish-white nodule 6 mm. in diameter resembling the nodules seen in the lung.

The tumor measured 20 by 12 by 6 cm. and lay in the right pelvis, extending up over the pelvic brim. It was entirely retroperitoneal with the right ureter running over its surface. The surface was smooth and regular, and the consistency was

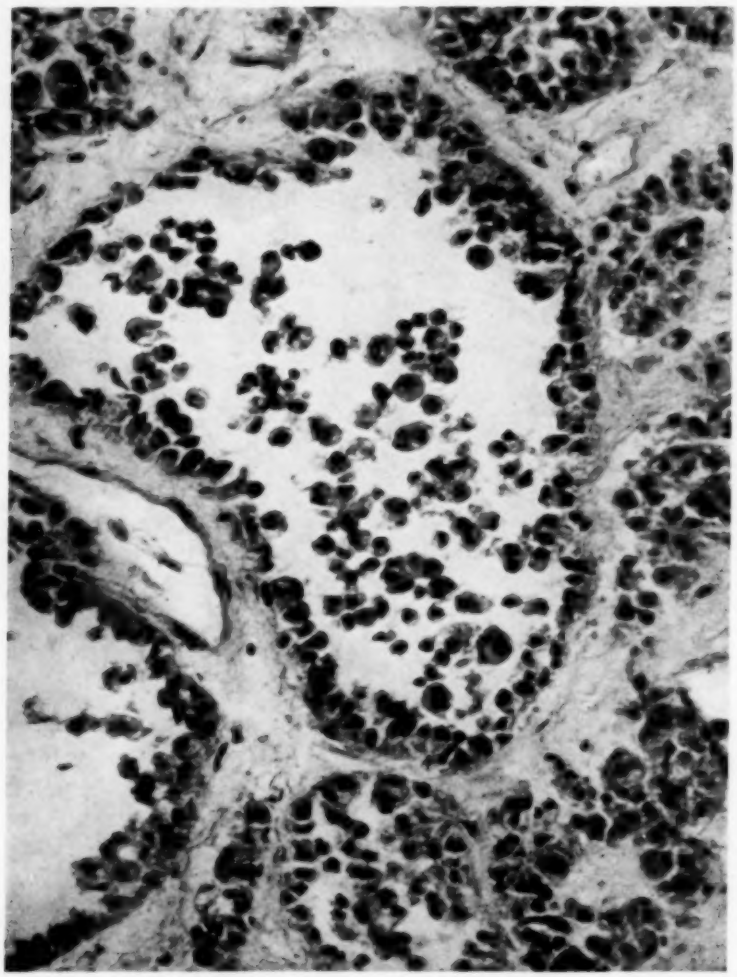

FIG. 8. Spaces in mucinous stroma lined by chordoma cells. (U. S. Army Medical Museum Neg. No. 68707, Acc. No. 60677 × 240.)

firm (figure 4). It was not adherent to any portion of the gastrointestinal tract. The tumor was easily freed laterally but was firmly adherent to the right psoas muscle and to the antero-lateral surface of the sacrum. After removal an area of erosion about 4 cm. in diameter was palpated at the point of attachment to the sacrum. The inferior vena cava and right iliac veins were dilated where they were pushed forward by the tumor.

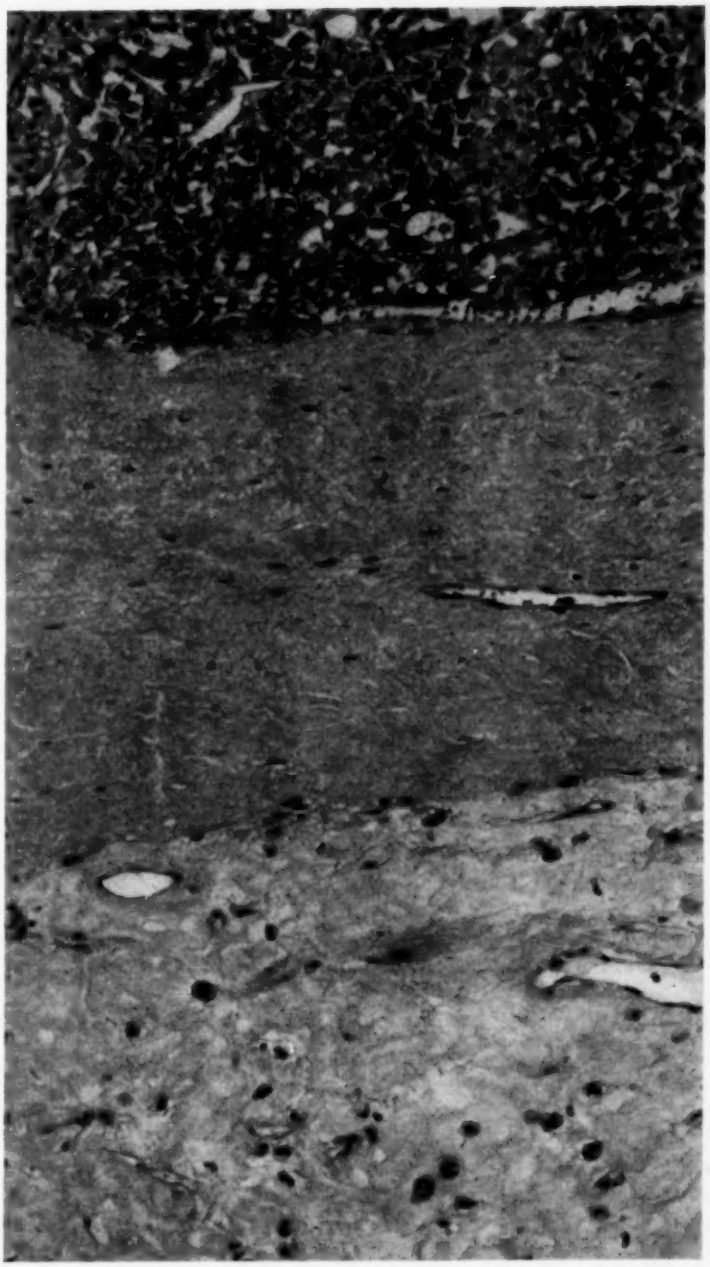

FIG. 9. Area showing almost acellular fibrillar material with scattered vacuolated chordoma cells giving the appearance of cartilage. (U. S. Army Medical Museum Neg. No. 68677, Acc. No. 60677 × 17.)

Sectioning of the tumor showed a coarsely lobulated surface with moderately soft, grayish-white areas separated by thick fibrous septa. In some areas these septa had a shiny, mucinous or cartilaginous appearance. Small cyst-like areas of degeneration were present and some areas showed a reddish-yellow color suggesting hemorrhage and degeneration (figure 5).

The skull was not opened.

Microscopic findings: The histologic picture varied. In some areas the cells were in compact masses with encircling, indistinct strands of supporting tissue which stained black with the Wilder silver stain. The tumor cells themselves were large, with pink staining (hematoxylin and eosin stain) granular cytoplasm and vesicular nuclei with a distinct nucleolus and scattered chromatin granules. Nuclei were rarely hyperchromatic and mitotic figures were not found. Cell borders were often indistinct, frayed or broken, leaving irregular clear areas in the cytoplasm (figure 6). Occasional cells presented distinct cytoplasmic vacuoles. Larger cells showed two to four nuclei. Some of the large cells were more acidophilic than others. Capillaries were rather numerous with occasional larger thin-walled vessels (figure 7). Areas of hemorrhage were present and some areas were necrotic. In other areas, elongated, cyst-like spaces were lined by tumor cells which were frequently in a single layer and stood out distinctly as individual cells supported by a thin strand of connective tissue (figure 8). The lumen contained varying numbers of unsupported cells. These cyst-like spaces lay in a matrix of pink staining, almost acellular fibrillar material. In some areas this pink staining material with scattered vacuolated tumor cells gave the appearance of cartilage (figure 9). With the Van Gieson stain this intercellular substance stained pale pink to a bright red, and a bright blue with the Masson trichrome stain.

A section, including a portion of the right psoas muscle, showed tumor cells among the muscle fibers and in several areas tumor cells were seen in vessels.

In sections of the metastatic lesions in the lungs, the tumor cells were in compact masses with little intercellular substance. Vacuoles were present in some cells, but there was no resemblance to cartilage.

The lesions in the left adrenal presented compact masses of cells, and also the cyst-like spaces seen in the primary tumor. Intercellular material was scant. All metastatic lesions were well circumscribed.

Mayer's muci-carmine stain showed no mucin in sections of the primary tumor or metastatic lesions.

Sections of the prostate and testes showed atrophy and fibrosis, probably secondary to radiotherapy. Microscopic examination of sections of the other organs was normal.

The histologic diagnosis of the tumor and metastatic lesions was chordoma.

Conclusions

1. Chordomata are tumors arising from remnants of the fetal notochord, which persist in the intervertebral discs and in the region of the spheno-occipital and sacrococcygeal articulations, and rarely in other regions adjacent to the skull and vertebral column. They may be relatively benign or more frequently malignant, with or without metastases. They may be amenable to surgical removal but usually it is a difficult procedure to remove the tumor mass completely, because of the location. Roentgen and radium therapy are of questionable value. A fatal termination in the course of one to six years is the rule, but cures have been reported following surgical removal.

2. The literature has been reviewed, and a case of a large malignant sacrococcygeal chordoma, extending into the right lower quadrant of the abdomen, with extensive pulmonary metastases and adrenal metastases, has been presented.

3. An outline of the clinical features of cranial, vertebral, and sacrococcygeal chordomata, with the histologic findings, has been presented.

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THE DIAGNOSIS AND TREATMENT OF CONGENITAL HEMOLYTIC (SPHEROCYTIC) JAUNDICE: REPORT OF A CASE WITH UNUSUAL BLOOD FINDINGS ALTERED BY LIVER THERAPY *

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Congenital hemolytic jaundice is a chronic blood dyscrasia generally characterized by microcytic anemia, acholuric jaundice, increased fragility of the red blood corpuscles to hypotonic salt solution, reticulocytosis, splenomegaly, and

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crises of hemolysis. It has frequently been stated that the victims are more jaundiced than ill. The belief that it follows a benign course, compatible with active and long life except when hemolytic crisis occurs, has been widely accepted. Many cases, however, do not follow this benign pattern.[1, 2, 3, 4, 25, 33, 36, 38] There is an increasing disposition to emphasize the more severe aspects of this disease [1, 2, 5, 33, 38]; and there is a changing attitude toward therapy, particularly toward blood transfusions [2, 5, 6, 29] and splenectomy.[1, 3, 4, 5]

The classification of many cases is difficult. The subdivision of idiopathic hemolytic jaundice into a congenital and an acquired type is not entirely satisfactory, since there is no agreement on the criteria to be used in making this separation. There are a number of observers who regard these two generally accepted types of the disease as clinical variations of the same entity.[4, 7, 8, 9, 10]

Many times an error in diagnosis occurs when symptoms of the disease are present. This is particularly true in children. The fact that the blood findings vary during short time intervals in the same case makes both diagnosis and classification difficult.

Our purpose is to report a case of congenital hemolytic jaundice exhibiting an initial macrocytic blood picture with normal fragility of the red blood cells and total absence of reticulocytes, and acute abdominal symptoms, in which the blood, after liver therapy, showed many microcytes and an increased fragility.

We also discuss this case and the literature with special reference to classification, diagnosis, blood picture after liver therapy, transfusion, and splenectomy. No attempt has been made to summarize the literature nor to harmonize that part discussed. It is too voluminous to permit the former and too conflicting and contradictory to permit the latter.

Case Report

The patient, a male, 21 years of age, was admitted to the Cornell University Infirmary one evening, after experiencing malaise, loss of appetite and energy for several days. Twelve hours before admission he had experienced initial severe pain in the left flank radiating around to the epigastrium, had felt "all in," and had passed several loose stools. The pain had been constant and consistently aggravated by movement. There had been no urinary symptoms.

For the previous two months he had experienced palpitation and shortness of breath on exertion, was easily fatigued, bothered by lack of concentration, and a tendency to worry. He had experienced one previous episode similar but not so severe, during January of 1939. At that time he had been confined to another hospital for three months and treated there solely for anemia. The hospital record showed that the hemoglobin had been reduced to 68 per cent and the red blood count to 1,900,000. The white blood count had been normal. No further investigations had been made. He had been given three transfusions with some improvement. No mention was recorded of adverse reactions to these. A definite diagnosis had not been made.

Diphtheria at three months and measles at the age of five years were the only illnesses previously encountered by the patient. Growth and development had followed a normal curve. The family history revealed that no analogous situations had occurred in the family. Mother, father, one sister, and a half brother were alive and well.

Physical examination revealed a well developed, fairly well nourished young male 21 years of age, obviously suffering severe pain. The skin and mucous mem-

branes were pale. There was no edema. The throat was slightly red. The cervical, axillary, and inguinal lymph nodes were palpable, discrete, slightly enlarged and tender. Examination of the chest was negative. Blood pressure (systolic) was 120 mm. Hg. There was tenderness in the left costovertebral angle extending around to the epigastrium and to the left upper quadrant where the muscles were so rigid that no intra-abdominal organs could be palpated. The white cells numbered 6,050; polymorphonuclears 66 per cent, lymphocytes 31 per cent, monocytes 3 per cent. The

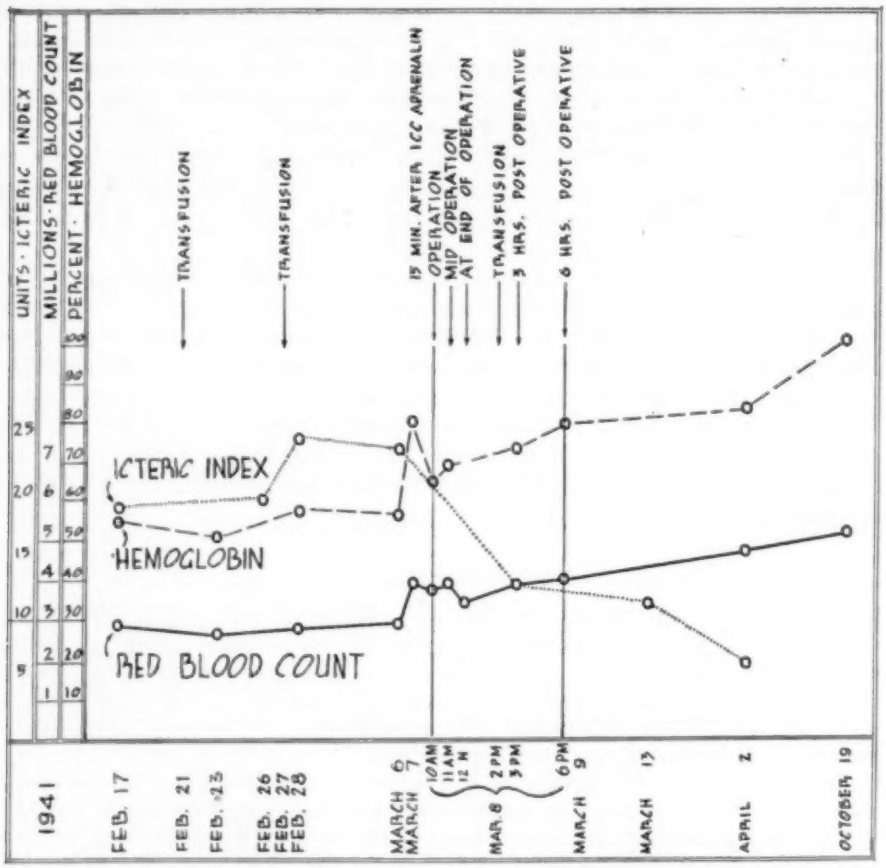

FIG. 1.

urine showed a slight trace of albumin. The temperature was 99, the pulse 88, and respirations 16. It was thought he might have the grippe.

In daylight next morning an icteroid tint was discernible. The blood then showed hemoglobin 61 per cent, red blood cells 2,820,000; CI 1.09; platelets 270,000; white blood cells 6,900; polymorphonuclears 59 per cent, lymphocytes 37 per cent, monocytes 2 per cent, eosinophiles 1 per cent. The icterus index was 21 units. The urine contained no bile, but urobilin was present. The peripheral blood showed no spherocytes. The blood smear closely resembled that of pernicious anemia. Many macrocytes and a few microcytes were present. There was a total absence of reticulocytes. The fragility test was equivocal, hemolysis beginning at .48 per cent saline, and was complete at .38 per cent (control range was from .46 per cent to .36 per cent

saline). It was at the time considered normal. Because of the blood picture, intensive liver therapy (1 c.c. concentrated extract intramuscularly daily) was administered for two weeks, but the anemia did not improve (figure 1). After the liver therapy there was, however, a striking change in the red blood cells and the fragility test. Many spherocytes appeared. The fragility range of the red blood cells changed to .50 per cent–.44 per cent saline (control .46 per cent–.30 per cent) and reticulocytes increased to 9.5 per cent. The icteric index was 19. Hemoglobin dropped to 53 per cent. The red blood count (2,790,000) remained at the previous level. Sternal puncture showed a normoblastic marrow. Gastric analysis revealed a total acidity of 4 units and a free HCl content of 2.8 units. Abdominal tenderness and rigidity had subsided during this time so that a mass in the left upper quadrant reaching almost to the umbilicus could be palpated. This was thought to be the spleen, and a diagnosis of chronic hemolytic jaundice of familial type in hemolytic crisis was made.

We were aware that severe reactions sometimes follow transfusions in these cases. Therefore, a small test transfusion was given without severe reaction and also without benefit. Indeed, 24 hours later the hemoglobin had decreased from 55 per cent to 53 per cent (figure 1) and the abdominal discomfort in the region of the spleen had increased. After one week had passed a larger transfusion (500 c.c.) was given. Twenty-four hours later the hemoglobin and red cells were slightly higher but the icteric index had risen from 20 to 26 units (figure 1). Abdominal discomfort had increased. We suspected that the transfusions had increased the hemolysis and that they had made the patient clinically worse.

Though it was recognized that the hemolytic crisis continued, immediate splenectomy was decided upon in lieu of further medical treatment. The patient had improved objectively and subjectively, but little improvement in the blood findings had occurred. The hemoglobin was 60 per cent; the red blood count was 3,020,000; and the icteric index was 24. To ascertain what improvement could be expected from the autotransfusion incident to the emptying of the spleen, a blood count was made 15 minutes after the intramuscular injection of 1 c.c. of adrenalin. The hemoglobin rose to 80 per cent and the red blood count to 3,870,000. Splenectomy was done without great difficulty on March 8. The spleen removed weighed 2178 grams. The gall-bladder was found to contain many small stones but was not disturbed. There were no accessory spleens. Dr. Henry Ferris, pathologist, reported "splenomegaly with intense congestion."

Blood studies made before, during, and after splenectomy showed striking changes. The preoperative hemoglobin was 61 per cent, red blood cells were 3,030,000. The icteric index was 24. A count taken at mid-operation showed the hemoglobin to be 68 per cent and red blood cells to number 4,000,000. At the end of the operation the hemoglobin was 70 per cent and the red blood count was 3,440,000. Three hours after splenectomy the hemoglobin was 77 per cent and the red blood count was 3,800,000. Six hours after the operation the hemoglobin had risen to 79 per cent and the red blood count to 3,900,000. Twenty-four hours after the operation the hemoglobin was 78 per cent and the red blood cells numbered 3,870,000. The icteric index was 12 units.

These findings corroborate the observations of Doan, Curtis, and Wiseman,[1, 3] both as to the rapid increase in red cells and hemoglobin during and after the operation as well as the rapid fall in the icteric index, the latter indicating a rapid decline in the rate of hemolysis. Sharpe[37] concludes that this immediate effect on hemoglobin and red blood cells is temporary and due solely to the autotransfusion incident to the emptying of the spleen.

Several hours after the operation the patient was given a transfusion for secondary shock from which recovery was prompt without adverse reaction. His con-

valescence was uneventful except for rather severe, protracted epigastric pain accompanied by some nausea and vomiting. This was attributed to gall-stones which were known to exist. His wound healed by primary union. He was discharged on April 16, the forty-third postoperative day. On that day the hemoglobin was 80 per cent and the red blood cells numbered 4,090,000. He was reëxamined October 19, 1941 and found to be in excellent condition, having gained 15 pounds in weight and having no subjective complaints. He was working as a truck driver, which required heavy lifting. He had experienced no palpitation or dyspnea, nor had he suffered any attack of abdominal pain. He did not tire easily. Difficulty in concentration was less evident. No retardation was noticeable. A blood examination showed the hemoglobin to be 102 per cent; the red blood cells to number 4,780,000; the white blood count to be 17,950; polymorphonuclears 76 per cent, lymphocytes 17 per cent, monocytes 4 per cent, eosinophiles 2 per cent, basophiles 1 per cent. The range of hemolysis of the red cells was from .48 per cent to .32 per cent saline. Many spherocytes (estimated 50 per cent) were present. There was a total absence of reticulocytes. The elevated white blood count was in part caused by contusions received in an automobile accident one day before the count. We considered him to be an example of cure following splenectomy. A letter from this patient received April 1, 1942 informed us that he had been accepted by the United States Army for military service.

We wish to emphasize the following features of this case and to discuss them with reference to the literature: (1) Classification and diagnosis; (2) the effect of liver therapy on the blood picture; (3) the fragility test; (4) reticulocytosis; (5) the effect of transfusions; (6) splenectomy.

Classification and Diagnosis

The hemolytic anemias cover a number of conditions which have been variously grouped and named. There is considerable variation in the designation of these diseases and some disagreement on classification. Although there is considerable disposition to regard the familial and idiopathic acquired type as variations of the same disease,[4, 7, 8, 9, 10] some authorities [40] still retain the old division into the congenital (Chaufford-Minkowski) type and the acquired (Hayem-Widal) type. The more recent suggestion of Thompson [12] to divide them into "spherocytic" and "the atypical type" is gaining adherents. The condition so long known as congenital or familial hemolytic jaundice in which the familial factor may be entirely masked or absent corresponds rather closely to Thompson's spherocytic jaundice, but there are discrepancies.

The diagnosis in children may be particularly difficult where, according to Debre et al.,[36] icterus and increased fragility are often lacking. Anemia is also sometimes absent. They point out that splenomegaly is the only constant feature. The fact that the blood picture varies in the same case at different times as in the case here reported makes diagnosis and classification in certain instances difficult. Riddle, in discussing Hill's work,[35] emphasizes this point. There also may be variation in any, or all, of the other symptoms, none of which is invariably observed.[20, 39] Pemberton [11] reports that Giffin at the Mayo Clinic found that 23 of 118 cases had been operated on for complicating gallstones before the diagnosis of primary hemolytic jaundice had been made.

Although we can discover no familial background, we believe that our case should be classified as one of congenital hemolytic jaundice. It also fits into Thompson's classification of "spherocytic anemia."

The spherocyte which is the basis of Thompson's classification was first described by Naegeli [14] who believed it to be pathognomonic of congenital hemolytic jaundice. Gaensslen [15] correlated the spherical nature of the cells with increased fragility, and Haden [16] considers that all other manifestations of the disease are secondary to the spherocytic nature of the red cells and that the primary defect is in the bone marrow. Meulengracht [40] does not agree with Gaensslen and cites cases with increased fragility of the red blood cells in which the red cell diameters are greater than normal (8.2 microns).

Thompson's impressions may be summarized as follows: Spherocytic jaundice is a uniform disease entity; the spherocytes are pathognomonic and take an active part in the disease process. All patients with spherocytic jaundice have spherical microcytes in their blood. These cells are directly responsible for the fragility in hypotonic salt solution. The cells of the blood are selectively removed from the general circulation in the spleen where they are found in greater numbers than in the peripheral blood. There is enough evidence to warrant the assumption that all the increased red blood cell destruction that occurs during the hemolytic phase takes place in the spleen. Diagnosis of the disease is possible from microscopic sections of the spleen alone, for the pathologic histology is specific. The symptoms of spherocytic jaundice are promptly, completely, and permanently relieved by splenectomy, although the spherical cells with their attendant fragility changes persist.

There are undoubtedly many cases like the one here presented that do not meet all of Thompson's requirements but are, however, in most particulars, identical with spherocytic anemia. Some cases with normal fragility and no spherocytes respond to splenectomy and behave as do the true spherocytic anemias. Other cases with spherocytes and increased fragility do not behave as spherocytic anemias and do not respond to splenectomy. There are instances in which the presence of spherocytes is not attended by increased fragility and also cases reported in which macrocytic blood shows increased fragility.[40] Dameshek [17] has had two cases of spherocytic jaundice which have failed to respond to splenectomy and one case in which the spherocytes and increased fragility disappeared after splenectomy. Hill [35] also cites cases in which these findings have disappeared after splenectomy. Dameshek [17] produces spherocytes and increased fragility experimentally by the injections of hemolytic agents. Van Boros [18] and Heilmyer [19] have found spherocytes and increased fragility in other conditions. It is apparent, as Hanrahan and Vincent [20] point out, that the designation of these cases does not lend itself kindly to over-simplification.

The Blood Picture and Liver Therapy

The initial blood picture in our case presented several unusual features: (1) a macrocytosis, anisocytosis, and poikilocytosis, (2) a lack of spherocytes with normal fragility, and (3) an absence of reticulocytes. The original smear and wet preparation seemed quite like those of pernicious anemia. Therefore, one c.c. of concentrated liver extract was given intramuscularly daily for two weeks. At the end of this period many spherocytes were observed and the fragility of the

red blood cells to hypotonic saline had increased. There are several cases reported [25] in which this change has taken place in the blood picture. One case is detailed by Riddle [35] in which the blood picture was followed through several changes. In the first phase the blood picture was that described as typical of familial jaundice. Some time later the blood presented a leukemoid picture with 40,000 white cells, many of which were myeloid in type and still later the blood picture was indistinguishable from that of pernicious anemia with macrocytosis, etc. The blood picture then reverted to the original one under liver therapy. Hill explains this macrocytic picture by assuming that during the long continued and excessive demand incident to increased erythropoiesis which exists in these cases the erythrocytic maturing factor is depleted. The supplying of this factor allows normal maturation of the red cells. This is especially apt to occur if cirrhosis or other damage to the liver exists.

Although it is true that liver therapy as a therapeutic measure to combat the anemia is generally considered useless and is said in certain instances to increase the hemolysis, it served a useful purpose in this case by producing a rapid change in the blood picture, thus lending material aid in the diagnosis. When blood pictures are atypical its use is justified on this basis alone. Reifenstein [21] feels that further study should be made before definite conclusions can be drawn regarding the efficiency of liver therapy.

The Fragility Test

An increased fragility of the red blood cells to hypotonic salt solution is said by certain observers to be pathognomonic of hemolytic jaundice. Dawson [2] states that the fragility is not altered in 10 per cent of the cases and others deny that it is a prerequisite to diagnosis. It is conceded to be an important diagnostic aid. These tests in our case showed little variation. In the initial test with a macrocytic blood, hemolysis began at .48 per cent saline and began in the control at .46 per cent, a difference of only .02 per cent. After liver therapy when spherocytes were present, hemolysis began at .50 per cent and began in the control at .46 per cent, a difference of .04 per cent. The first test was interpreted as normal and the second as showing a decreased resistance. After splenectomy hemolysis appeared again in .48 per cent saline and in the control in a .46 per cent solution. At this time there were many spherocytes present.

It is evident that a test which is as important as the fragility test is thought to be, should be carefully controlled; yet we find controls rarely mentioned in the literature. In a series of cases Watson [32] found that hemolysis in normal controls began in concentrations of saline varying between .54 per cent and .38 per cent. The finding of such wide variation in normal controls makes it difficult to interpret such small differences as .02 per cent and .04 per cent between beginning hemolysis of the patient's blood and that of the control. Such difficulty existed in our case.

From these figures and the variation of those reported elsewhere, it seems reasonable to question the reliability of the test as it is usually done. We doubt if it is reliable enough to be dependable as a major diagnostic point.

Doan, Wiseman, and Erf,[22] after critical analysis, conclude that fragility tests done with hypotonic saline are universally unsatisfactory even under the best controlled conditions. If a test were accurate, we should expect less divergent

results in normal controls. Wiseman and Bierbaum [23] have devised and described a test using distilled water instead of saline which seems more accurate. There is almost no variation exhibited among normal controls in the point at which hemolysis begins. The value is almost constant. They express their results in saline equivalents, the normal limits being 0.300 to 0.412 per cent. These limits thus sharply defined have been found so generally under normal conditions that any deviation in either direction may be interpreted as an abnormality. The only control necessary is a specimen of the patient's whole blood to be certain that no hemolysis has occurred in the collection of the specimen. The information we really want when we do a fragility test is the degree of stability of the red cells of a given patient in that patient's own serum. Their test seems to give this information.

The following statements concerning the red cell fragility seem justified: (1) the fragility in hemolytic icterus varies in different subjects; (2) it varies in the same individual at different times; (3) an increased fragility is the usual finding but it is not necessary in order to make the diagnosis; (4) it is not pathognomonic of the disease when it is present.

Reticulocytosis

Reticulocytosis is said to be a prominent feature of the blood picture in hemolytic jaundice. It is considered to be of important diagnostic significance.[13] In general the more active the hemolytic process, the higher the reticulocytosis.[13] It may even be so pronounced that it dominates the blood picture. It has been said that the fluctuations in the disease may be followed by the rise and fall of the reticulocyte counts. Although the average is between 20 per cent and 30 per cent,[12] a count above 50 per cent is not unusual. Baty [24] reports a patient in whom the reticulocytes reached 92 per cent, and Reynolds [25] one whose reticulocytes reached 95 per cent. Tileston [34] states that reticulocytosis exists to a far greater degree than found in any other disease. Vital staining in our patient revealed an initial total absence of reticulocytes, and only 9.5 per cent were found after liver therapy. It is interesting to note that a number of normal reticulocyte counts [26, 27, 28] are recorded but we found the report of no case which presented a total absence of these cells.

Transfusions

It would be quite natural to assume that the treatment for a chronic disease marked by anemia, oftentimes rapidly progressive, not responding to iron, arsenic, or liver, would be transfusion or repeated transfusion. Although many authors do not mention it, an increasing number [1, 2, 5, 6, 13, 29, 30] are not only impressed by the lack of benefit derived from transfusions but they point out that increased hemolysis and aggravation of clinical symptoms often follow, and also that in certain cases even death may ensue. In our case the patient was given three transfusions (figure 1) all from the same donor whose blood was of the same type. The first or "pilot" transfusion of 200 c.c. was followed by slight aggravation of abdominal discomfort and a definite fall in the hemoglobin (figure 1). After the second larger transfusion (500 c.c.) there was even more increase in abdominal pain and some elevation of heart rate. Although there was a slight

gain in hemoglobin and red blood cells at the end of 24 hours, the icteric index had risen from 20 to 26 units indicating an increased hemolysis. There was no evidence of any reaction when 450 c.c. of blood were given to him six hours after splenectomy.

Baker and Dodds [6] record a fatal case in which several transfusions had been given, followed each time by high temperature, nausea and vomiting, and deepening jaundice. Autopsy revealed the kidney tubules blocked by acid hematin. Dawson of Penn [2] warns of the danger. Dameshek [13] mentions several reactions following the use of a donor of the same type as the recipient. Doan [5] is emphatic in his statements concerning the dangers of transfusion, and the fourteenth edition of Osler [30] mentions it. Some conclude that transfusion is contraindicated. Kilduffe and De Bakey [31] feel that severe reactions are unusual but that preserved blood should not be used. Our experience with this case and a perusal of the literature lead us to believe that the profession in general does not yet appreciate the grave dangers that may accompany transfusions in hemolytic jaundice. We advocate extreme caution and suggest a small "pilot" transfusion as advised by Dawson.[2]

Splenectomy

Although splenectomy is the accepted method of treatment and is said to be regularly curative in a clinical sense, there was until recently all but universal agreement that the operation should not be done during a hemolytic crisis. However, an occasional death occurs before remission from hemolytic crisis in spite of all other treatment.[2, 36, 38] In cases like this, it is the contention of Doan, Curtis, and Wiseman [1, 3] that not only is splenectomy desirable but an emergency splenectomy is imperative. They report five cases of congenital hemolytic jaundice in acute fulminating crisis with red cells at or below 1,000,000 in which splenectomy was carried out. There were no fatalities and in each case there was a dramatic rise in the hemoglobin and red blood cells while the patient was still on the table. There was an immediate cessation of hemolysis. This immediate and striking improvement occurred in every case. They feel it can be relied upon and that splenectomy under such circumstances is a life saving measure. In the case here reported, splenectomy was done during a hemolytic crisis and a dramatic effect on the blood picture and hemolysis (figure 1) was observed. Dameshek and Schwartz [13] also advocated emergency splenectomy in certain cases of acute acquired hemolytic anemia (Lederer's anemia), a type which has been accepted as one which usually responds dramatically and permanently to transfusions. Debre [36] advocates splenectomy in infants and children before puberty because the disease may produce infantilism, skeletal deformities and mongoloid features in these patients. Krumbhaar [7] feels that the advice to operate during crisis without waiting for remission or benefit of transfusion should be followed with caution and reluctance. It seems reasonable, nevertheless, to admit that our ideas concerning splenectomy during a crisis in either the congenital or acquired type of hemolytic jaundice may be in need of revision; and that in certain carefully selected cases splenectomy is not only advisable but positively indicated.

Summary

1. A case of hemolytic jaundice in hemolytic crisis is reported in which the blood exhibited a macrocytosis, normal fragility and total absence of reticulocytes at the time of initial examination of the red cells.

2. A spherocytic blood picture with increased fragility and 9.5 per cent reticulocytes appeared after liver therapy.

3. Splenectomy during a crisis was followed by an immediate dramatic rise in hemoglobin and red cells and an abrupt cessation of hemolysis.

4. Transfusions were cautiously given without severe reaction, but with definite signs of increased hemolysis.

5. A warning is sounded concerning transfusions in hemolytic jaundice.

6. Favorable opinion is expressed regarding "emergency splenectomy."

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ACUTE HEMOLYTIC ANEMIA WITH TOXIC HEPATITIS CAUSED BY SULFADIAZINE; REPORT OF A CASE *

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Acute hemolytic anemia resulting from the use of sulfonamides has been frequently reported. Long, Haviland, Edwards and Bliss,[1] in a large series, noted its occurrence in 1.8 per cent of cases following the administration of sulfanilamide and in 0.6 per cent after sulfapyridine. This toxic effect was not seen with sulfathiazole.

Rothstein and Cohn,[2] however, have recently reported one case, and Bunim and Israel [3] two cases following sulfathiazole.

Sulfadiazine has been considered innocuous as far as the hematopoietic system is concerned. Mild anemias may occur, but to date no case of hemolytic anemia following its use has been reported. For this reason we believe it important to report the following case of acute hemolytic anemia and toxic hepatitis following the administration of sulfadiazine.

Case Report

E. P. W., a white male, age 47, was admitted to Harper Hospital on March 8, 1942 with a history of rhinorrhea, sore throat, generalized aching and malaise for one week. Twenty-four hours previous to admission he had a chill, sharp pain in left chest accentuated by respiration, cough productive of purulent, rusty sputum and nausea and vomiting. No chemotherapy had been attempted before admission.

Physical examination revealed an acutely ill patient, pale and dehydrated, temperature 103.4° F., respirations 36, pulse 132, blood pressure 68 mm. Hg systolic and 34 mm. diastolic. The pharynx was acutely injected; the chest showed dullness to percussion, tubular breathing, moist râles, and a pleural rub over the left base posteriorly and left axilla. Other positive findings included poor cardiac tones with a soft systolic murmur (this latter present over a number of years), and slight abdominal distention. Initial blood count: hemoglobin 92 per cent; red blood cells 4,450,000; white blood cells 11,000, with 89 per cent polymorphonuclears and 11 per cent lymphocytes. Sputum typing showed types III and V pneumococci on March 9, 1942. Sputum pneumococcus count (March 9, 1942—method of Drs. Price, Frisch, etc.[4]) showed s.s.s. reticular network, clumping with some phagocytosis and 10 organisms per high power field.

An admission diagnosis of left lower lobe pneumonia was made and patient given sodium sulfadiazine intravenously 2.5 gm. twice at two hour intervals on March 8, 1942, followed by sulfadiazine, 1.0 gm. orally at four hour intervals day and night with 10 gm. sodium bicarbonate with each dose.

Roentgenogram on March 10, 1942 confirmed the diagnosis of left lower lobe lobar pneumonia.

The clinical course showed slight improvement in 48 hours, an oxygen tent being used after the first 24 hours, but the temperature remained about 101° F., and on March 11, 1942, because of low drug levels, sulfadiazine was increased to 1.5 gm. every four hours and the patient was also given 80,000 units of type V antipneumococcic rabbit serum intravenously.

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From the Medical Clinic of Harper Hospital, Detroit, Michigan.

On March 12, 1942 there was evidence of extension to the right base. Hemoglobin was 78 per cent; white blood cells numbered 13,500. On March 13, 1942, hemoglobin was 74 per cent; white blood cells numbered 14,850.

On March 14, 1942 the temperature had gradually dropped to 100° F., and sulfadiazine was reduced to 0.5 gm. every four hours. Hemoglobin was 69 per cent; white blood cells numbered 19,000.

Early on March 15, 1942 the temperature rose to 101° F., and it was felt that there was probably an extension of the process in the left lung. Therefore, sulfadiazine was increased to 1.5 gm. every four hours. By the following morning (March 16, 1942) the temperature was 103.6° F., and definite icterus was present. The liver was palpable and tender. The leukocyte count rose to 30,000; hemoglobin was 71 per cent. Sulfadiazine was stopped immediately. In eight days 59 gm. of the drug had been given, with blood levels ranging from 5.2 to 11.1. On March 16, 1942, the last day of treatment, the level was 10.7.

On March 17, 1942 the icteric index was 35; the Van den Bergh reaction was positive—direct and indirect.

Hemoglobin had dropped to 53 per cent, red blood cell count to 2,666,000, white blood cell count to 25,550. It was clear that a severe hemolytic anemia with toxic hepatitis had developed, and as with other sulfonamides, the hemolytic process was preceded by a sharp rise in leukocytes.

Blood transfusion was decided upon. The patient was found to be a type IV, and the department of hematology reported numerous cross agglutinations with potential donors of type IV, with the constant finding of agglutinations of the donor's cells by the patient's serum. It was finally decided that this phenomenon must be due to the presence of atypical agglutinins. Tests were then made for the so-called cold agglutinins. A suspension of the donor's cells in the recipient's serum was placed in the refrigerator with heavy agglutination resulting. The same suspension was then incubated at 37° C. for five minutes, with the result that the agglutination was completely broken up and a satisfactory reaction obtained. It was found that this process could be repeated at will by taking the same mixtures and alternately placing in the ice box and incubator. Furthermore, the same reaction occurred when the patient's cells and serum were mixed, indicating the presence of auto-agglutinins.

On March 17, 1942 transfusions were started and 250 c.c. of citrated blood were given on five occasions without reaction of any kind.

Other treatment consisted of fluids forced orally and parenterally, thiamine chloride 50 mg. intravenously, liver extract 1 c.c. intravenously and ferrous sulphate, 1 gm. by mouth daily. A high carbohydrate diet was administered.

The patient's course was stormy for several days, with increasing anemia. However, by March 24, 1942 improvement began, the icterus lessened and the blood picture improved. Temperature became normal on the eighteenth hospital day.

Subsequent blood studies were as follows: (3–19) Hemoglobin 34 per cent. Red blood cells 2,170,000. (3–20) Erythrocyte fragility: hemolysis began at .50 per cent, ended at .30 per cent. Reticulocyte count 4.5 per cent. (3–24) Hemoglobin 45 per cent. Red blood cells 2,340,000. (3–27) Hemoglobin 58 per cent. Red blood cells 2,890,000. (4–8) Icteric index 6. (4–13) Hemoglobin 77 per cent. Red blood cells 3,940,000.

The patient was discharged on April 13, 1942. Chest findings were entirely negative. Icterus had cleared and liver edge was no longer palpable. A slight anemia still existed.

Summary

A case of acute hemolytic anemia with toxic hepatitis following the administration of sulfadiazine (59 gm. in eight days) is reported. To the best of our

knowledge there are no previous reports of this occurring, and for this reason we feel it important to call attention to this possible danger.

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SPONTANEOUS PNEUMOTHORAX AND BRONCHIAL ASTHMA *

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The increase in diagnostic acuity during the past few decades has demonstrated the fact that relatively few cases of spontaneous pneumothorax are due to tuberculosis. On the other hand, factors which cause increased intra-alveolar pressure and thinning of the alveolar wall are almost uniformly present in chronic asthmatic patients. One would then anticipate, a priori, that spontaneous pneumothorax would be a frequent complication in these individuals. An inquiry into the literature on this subject has failed to reveal more than 20 such instances, and, of this number, only two have been verified by autopsy (table 1).

Recently our attention has been directed to a case which presented the characteristics of this symptom complex.

Case Report

The patient was a 48 year old, white male, who entered the hospital on September 14, 1941, complaining of marked dyspnea of three weeks' duration. He stated that for about 20 years he had had a chronic productive cough. A year and one-half prior to entry he had been ill with pneumonia. Following this he had an attack of asthma which recurred three or four times subsequently. About three weeks before hospitalization he rather suddenly developed severe dyspnea and orthopnea. During the two weeks immediately preceding admission his feet and ankles had been swollen and he had lost several pounds in weight. There is no record of episodes of hemoptysis or chest pains. His family history and past history are irrelevant.

The physical examination revealed a poorly nourished, acutely ill patient, unable to breathe lying down. His temperature was 98.4° F., pulse 140, respirations 46, and blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The trachea was displaced

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From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana, New Orleans, Louisiana.

to the left. Although the lungs expanded equally on the two sides, the respirations were shallow and labored. Over the right lung field there were hyperresonance, diminished tactile fremitus and diminished breath sounds. Moist râles were heard over the lower halves of both lung fields. The cardiac border was markedly displaced to the left and there was a systolic murmur over the pulmonic area. There was pitting edema of both feet and ankles.

TABLE I

Authors	Age of Patient	Sex	Duration of Asthma	Affected Side	Duration of Pneumothorax	Course	Results
Debove[12]	27	Male	Since infancy	Left	Few days	Without effusion	Cure
Emerson-Beeler[13]	22	Female	Twenty years	Bilateral	Six months	Without effusion	Death*
Spivake[15]	11	Female	Nine years	Left			
Kahn[14]	36	Female		Left	Three months	Without effusion	Cure
Fernet[11]	43	Female	Twenty-eight years	Right	Few days	Without effusion	Death*
Pastorino[12]	28	Male	Six years				
Dainini-Alvarez[12]	19	Male	Few years	Left		Without effusion	Cure
Casiello[12]	53	Male	Few years	Right	Four and ½ yrs.	Without effusion	Cure
Castex-Mazzei[4]	25	Male	Thirteen years	Left	Four and ½ yrs.	Without effusion	Cure
McGuire[15]	27	Female	Few years	Left		Without effusion	Cure
Faulkner-Wagner[12]	59	Male	Number of years	Left		Without effusion	Death
Laennec[12]	30	Male		Bilateral		Without effusion	Death
Harvey[6]	19 25	Male Female	All of life Three years	Left Right	One month	Small effusion	Cure Cure
Bottero[16]	45 88	Male Female	Four years Since birth	Left Left		Without effusion Without effusion	Cure Cure
Casoli, Alvarez and Pedroza[17]	54	Male			Thirteen months	Hydropneumothorax	Death
Elliott[18]	44	Female	Nineteen years	Right		Without effusion	Cure
Jeffrey and Morlotte[19]	17	Male	One year	Left at first, then bilateral		Without effusion	Cure
Fuchs[20]	27	Male	One year	Right			Cure

* Autopsy.

Laboratory Findings. The hemoglobin was 80 per cent, red blood cell count 4,700,000, white blood cell count 10,250, with 63 per cent polymorphonuclear leukocytes, 3 per cent eosinophiles and 34 per cent lymphocytes. The urine contained a trace of sugar and three or four white cells per high power field. The Kline and Kolmer tests were negative. No acid-fast bacilli were found in the sputum. A roentgenogram of the chest showed 50 per cent collapse of the right lung and mottling in the first interspace on the left.

Clinical Course. The patient was thought to have a right pneumothorax and bronchial asthma. Thoracentesis was done, and 200 c.c. of air were withdrawn from the right hemithorax. The patient's general condition grew worse and he began to have periods during which he could not be aroused. On September 16, a blowing sound was heard over the right side of the chest and was thought to indicate a possible bronchopleural fistula. Thirteen hundred cubic centimeters of air were withdrawn

from the chest on this day. The patient's condition varied. At times he was comatose and unable to respond, whereas on other occasions he was able to feed himself. Aspiration of his chest was done repeatedly. The patient died suddenly on September 18, the temperature having remained practically normal until the day before his death.

At autopsy the outstanding pathologic changes were found in the heart and lungs. The heart weighed 320 gm., and its measurements were as follows:

T. V. 13.0 cm.	P. V. 8.0 cm.	R. V. 0.2 cm.
M. V. 8.5 cm.	A. V. 7.5 cm.	L. V. 1.6 cm.

The heart was not enlarged. Its pericardial and endocardial surfaces were smooth and shiny and the right ventricular wall was somewhat thickened, and the ventricle dilated as well. The valves were thin and freely movable. The coronary vessels contained small atheromatous plaques, and one calcified area was found in the left anterior descending artery. The musculature was reddish-brown and uniformly firm. No fibrosis was grossly visible.

On microscopic examination the pericardium was found to be normal. The muscle fibers were uniform in size and staining character and there were visible pigment granules at the ends of the nuclei. There was no marked increase in fibrous tissue and the coronary vessels showed atheromatous changes.

The right lung weighed 550 gm., and the left 390 gm. The right lung was small and somewhat wrinkled on its surface, which was marked by fibrous adhesions and by occasional emphysematous blebs. At the apex some of these blebs were collapsed. The cut surface of the right lung had a mottled gray appearance and the bronchi were also prominent on this side.

The pleura was thickened by dense scar and fibrous tissue. In the majority of the sections the alveoli were partially collapsed and they contained numerous pigment-bearing macrophages. In a few areas the alveoli were widely dilated, the walls being thin and frequently ruptured. Many of them contained fibrin, lymphocytes and polymorphonuclear leukocytes. All the bronchi were dilated, the fibrous tissue around them being hypertrophied and heavily infiltrated with lymphocytes. Some of the bronchi contained large numbers of polymorphonuclear cells. There was one area in which there had been considerable hemorrhage into the alveoli.

Pathologic Physiology

As early as 1887 West [1] demonstrated that the normal pleura does not rupture until the intrapulmonary pressure exceeds 200 mm. of mercury. Inasmuch as such tension cannot be produced by the most severe paroxysms of coughing, rupture of the pleura presupposes some anatomic or pathologic alteration at the site of rupture.

Emphysema is a common complication of bronchial asthma. Kjaergaard,[2] in an extensive and thorough inquiry into the subject of spontaneous pneumothorax, was able to incriminate emphysema as the etiologic agent in only seven out of 918 cases. It is paradoxical to consider that the distention and atrophy of the lung tissue, so characteristic of emphysema, may result in extreme thinning of the alveolar wall without rupture. Studies on this problem by Zahn [3] have shown that, although the thickness of the alveolar wall plus that of the visceral pleura is normally 0.13 to 0.24 mm., in emphysematous lungs it may diminish to 0.05 or even 0.03 mm. Castex and Mazzei [4] offer, as an explanation for the rarity of rupture of the emphysematous lung, the progressive decrease in the negativity of the intrapleural pressure which occurs. Finally the intrapleural pressure be-

comes nearly positive and an equilibrium tends to be set up between the intrapleural and intra-alveolar pressure. Thus it would appear that a protective compensatory mechanism operates to establish a steady state.

On the other hand, factors exist which may weaken the particular zone of the lung which yields. Thus, a destructive process such as tuberculosis, congenital cysts, congenital valve vesicles, emphysematous valve vesicles, and cicatricial valve vesicles [5] may coincide with the asthma. If the spontaneous pneumothorax is due to an erosive process resulting from the caseous destruction of lung tissue, it would be followed by pleural infection and pyopneumothorax, but this has never been shown. As Wilson [5] has aptly stated, the mechanism of actual rup-

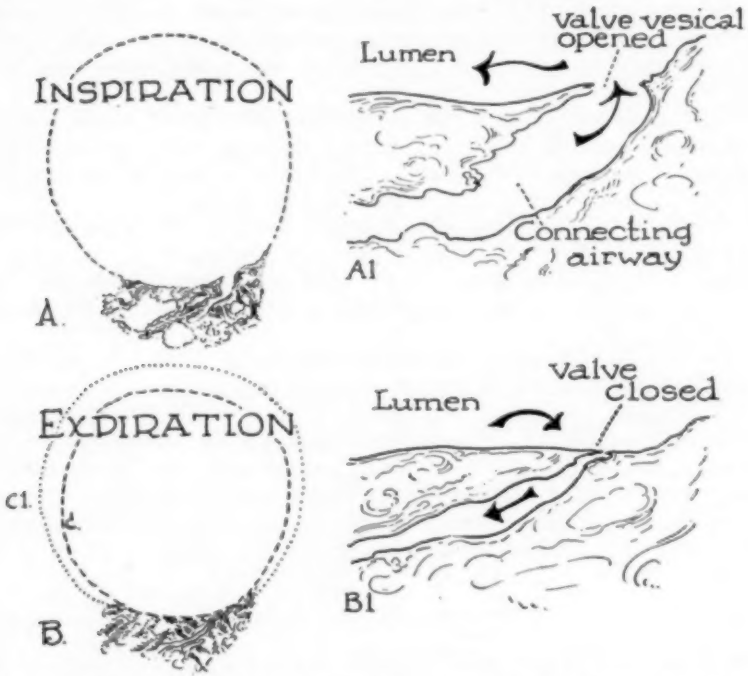

FIG. 1. Schema demonstrating the mechanism involved in the progressive increase in size of the valve vesicles.

ture is apparently the same in any of the above pathologic states. We believe that the rupture occurs through the intermediation of a valve vesicle, whatever its etiology may be. With each respiratory cycle the positive pressure increases in the valve vesicle because the nature of the lesion allows air to enter with greater ease than to leave (figure 1). In this manner a vicious cycle is initiated, so that the pleural covering of the vesicle becomes progressively thinner and, because of diminished blood supply, devitalized. Then, without any appreciable strain, the vesicle tears and a greater or lesser degree of pneumothorax results.

It has been suggested, and we believe rightly so, that the danger of rupture is greater on deep inspiration than on coughing, because then there is atmospheric pressure within the alveoli and a negative pressure without. During coughing the tendency is toward the closer approximation of the chest wall to the lung, re-

sulting in a decrease in negativity in the intrapleural space and a lessening of the positive pressure in the alveoli. Both of these factors act to preserve the integrity of the vesicle. Coughing, however, could tear the lung in marginal zones where the pressure is unequal.[6]

Whereas spontaneous pneumothorax can happen at any age, it usually occurs in early adult life. It is at this time that negative intrapleural pressure is greatest. In the first place the elastic recoil of the lung is greater in youth; secondly, the action of the diaphragm is more efficient in early life because, with increasing age, the central tendon becomes more fibrous, occupying a larger proportion of the total mass of the diaphragm, and, finally, the degree of emphysema is less.

Kjaergaard[2] and Hayoshi[7] have demonstrated, by means of postmortem studies on individuals dying from a variety of causes, that valve vesicles, already alluded to, actually occur. It was found that these vesicles were situated most commonly at the apices. In our case, both tear and vesicles were found in the apex.

The opinion that the most common etiologic cause of pneumothorax is tuberculosis is widely shared. Whereas tuberculosis is an etiologic factor in the causation of pneumothorax, it is the opinion of Wilson[6] and others,[8] who have had a wide experience, that tuberculosis accounts for not over 10 per cent of the cases. It may be emphasized again that no gross or microscopic evidence of active tuberculosis was demonstrated in our case. In this respect it should be pointed out that the process of healing in tuberculosis may be associated with valve vesicle formation, especially at the apices.

Diagnosis

The physical signs of pneumothorax associated with asthma do not differ from those of other etiology. The symptoms of pain, cough, dyspnea and shock are found. The first and most important physical finding is suppression of fremitus, breath and voice sounds. Hyperresonance and displacement of the heart are often demonstrable. The roentgen examination, of course, is the sine qua non of the diagnosis and without its aid many cases of minimal pneumothorax would be overlooked. This possibility should be kept in mind, particularly when the asthmatic patient complains of sudden sharp chest pain with, or without, dyspnea. The use of the tuberculin test is of great value because, when it is negative, the prognosis is extremely favorable. The main point in the differential diagnosis is the exclusion of the tubercle bacillus as the etiologic agent. Little confusion could arise in the diagnosis of traumatic pneumothorax and of that complicating pulmonary infarct, bronchiectasis, or of pulmonary abscess where the primary underlying cause should be easily recognized.

Prognosis and Treatment

The prognosis in cases of pneumothorax complicating asthma is very good. As a matter of fact the condition is probably of much more frequent occurrence than has been generally appreciated. Its benignancy is attested by the fact that there are not more than three instances of postmortem studies, including our own. The nature of the underlying lesion is such that the recurrence of spontaneous pneumothorax is not common, and pulmonary tuberculosis, as a sequel, must be considered to be exceptionally rare.

Masterful neglect is the keynote of treatment because, with a minimum of therapy or none, the vast majority of these patients recover, provided the patient is not in an acute asthmatic attack. The cough may require mild sedation and, depending upon the severity of the pain, codein may be administered.

The removal of air from the pleural space has been advocated, and was practiced in the case here reported. We feel that this measure is strongly contraindicated for three reasons: (1) The equality of pressure within and without the alveolus facilitates healing of the torn vesicle; (2) removal of air and the production of a negative intrapleural pressure favor the formation of a bronchopleural fistula from which a chronic pneumothorax, or a tension pneumothorax may result; (3) the existence of a fistula favors the contamination of the pleural space. Tension pneumothorax appears to be the one indication for thoracentesis. Here action is imperative with the end in view of relieving the patient's respiratory distress rather than expanding the lung. Therefore, we advocate that these cases be treated conservatively by bed rest, for a period of two to six weeks' and with mild sedation as required.

After the site of rupture has healed, the use of air-oxygen mixtures where the concentration of oxygen approaches 100 per cent may be of real value. Fine [9] and his associates have advocated this based upon the experimental work of Shaw.[10] It will be remembered that the oxygen fraction of the air in the pleural space is rapidly absorbed, but the nitrogen fraction remains. This latter gas disappears from the tissue spaces very slowly because its diffusibility into the blood stream depends upon the small difference between its partial pressure in the tissue spaces (627 mm. of mercury) and the blood (573 mm. of mercury). Shaw [10] measured the fall of the partial pressure of nitrogen in the arterial blood during the inhalation of pure oxygen and found that after one hour pressure was 155 mm. of mercury, after two hours 91 mm. of mercury, after three hours 52 mm. of mercury and after four hours 31 mm. of mercury. Therefore, as Fine and his collaborators have pointed out, when pure oxygen is breathed the diffusion pressure existing between nitrogen in the tissues and that in the blood progressively increases so that one should expect a corresponding increase in the speed of absorption of nitrogen from the tissues into the blood stream whence it escapes into the expired air. Indeed, experimental evidence has been offered confirming these theoretical considerations.

If, however, the patient is having an attack of asthma, one uses the customary antispasmodic drugs, with the end in view of relieving the acute paroxysm as rapidly as possible. After the acute episode has subsided, an attempt is made to determine whether the asthma is of the intrinsic or extrinsic variety. If it is of the latter type a search is made for the offending substances, by a combination of a careful history and proper skin tests.

Materials for testing should be selected in view of the circumstances surrounding the case. For this purpose the history may be of inestimable value in directing the attention to certain possible causative agents. Further proof of this relationship is obtained by positive skin reactions to non-irritant diagnostic solutions, or at times by means of therapeutic trial.

The specific method of treatment is dependent on the etiologic factors unearthed by the diagnostic survey. It may be summed up, then, by saying that therapy consists in the elimination of the offending agents whenever this may be

done. When this is not feasible for one reason or another, specific or non-specific desensitization is inaugurated. Numerous forms of non-specific therapy are also employed.

Summary

A fatal case of spontaneous pneumothorax in an asthmatic patient has been described. An attempt has been made to explain the mechanism involved, and on the basis of this, the etiology, physiology, symptomatology, diagnosis and treatment are discussed.

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EDITORIAL

SALICYLATES IN THE TREATMENT OF RHEUMATIC FEVER

ALTHOUGH salicylates have been used in the treatment of rheumatic fever for nearly seventy years, there is still a wide divergence of opinion as to the degree of their effectiveness. There is no doubt as to their ability, even in moderate doses (up to six grams a day), to relieve the pains of arthritis, to alleviate the local manifestations of inflammation in the joints and usually to control the fever, at least temporarily. There is also general agreement that they do not exert a direct destructive action on the infectious agent. There is more difference of opinion as to their influence on the vascular and cardiac lesions. Thus far, however, there has been no convincing proof that salicylates significantly reduce the incidence of such lesions. This is a crucial point in treatment, since the disability and mortality in rheumatic fever are so largely a result of vascular and cardiac injury.

This uncertainty is due in part to ignorance of the mode of action of salicylates, and to rather haphazard methods of administration, as well as to the previous lack of means of precisely controlling their administration. Another difficulty has been the lack of knowledge of the etiology and pathogenesis of the disease itself.

Although no infectious agent has yet been demonstrated in rheumatic fever, there is considerable indirect evidence that hemolytic streptococci are in some way involved. It is well known that an acute streptococcal pharyngitis often precedes an acute attack of rheumatic fever by one to three weeks. Also a marked increase in titer of circulating antibodies, particularly of antistreptolysins, accompanies an acute attack. No living agent has been demonstrated in the joints or tissues of the cardiovascular system, however, and if a streptococcus is really the etiological agent, its action must be exerted in some indirect way.

Many investigators have suggested that the local lesions in the tissues in rheumatic fever are manifestations of an allergic or anaphylactic reaction. Attempts to reproduce the lesions by injections of bacteria into sensitized animals have not led to convincing results. Recently, however, Rich and Gregory [1] have reported the production of lesions showing the fundamental characteristics of those of rheumatic fever by producing serum disease in animals. They [2] have also pointed out the close resemblance of the pulmonary lesions in rheumatic fever to those in cases of hypersensitiveness to sulfonamides.

[1] RICH, A. R., and GREGORY, J. E.: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity, Bull. Johns Hopkins Hosp., 1943, lxxiii, 239–264.

[2] RICH, A. R., and GREGORY, J. E.: On the anaphylactic nature of rheumatic pneumonitis, Bull. Johns Hopkins Hosp., 1943, lxxiii, 465–478.

Coburn and Pauli [3] have furnished indirect evidence of another type in support of this view. They showed that a positive precipitin reaction occurs when serum obtained during the acute phase of rheumatic fever is mixed with serum obtained during the symptomless period of about two weeks ('phase 2') that intervenes between the initial pharyngitis and the acute outbreak. They interpret this as indicating that during the symptomless period (which might be regarded as the incubation period) the serum contains precipitinogen, presumably produced by the streptococci in the pharynx. At the onset of the acute phase, antibody (precipitin, antistreptolysin) appears in quantity in the plasma, and they have found an approximate correlation between the antibody titer and the severity of the attack. The tissue inflammation they regard as the result of a reaction, anaphylactic in type, between this antibody and the circulating antigen.

The action of salicylates in alleviating the inflammation and the symptoms associated with it must be accomplished, they think, by interfering in some way with this reaction. Coburn and Kapp [4] carried out some in vitro experiments to test this hypothesis. They found that salicylates did diminish the amount of precipitate formed when horse serum euglobulin or egg albumin was mixed with the corresponding antiserum. This inhibition appeared to be due to interference with the antibody. A relatively high concentration of salicylate was required, however, and its inhibitory action was diminished if an excess of antibody was present.

These observations suggested that if salicylates act in the same way in vivo, their effectiveness in rheumatic fever would depend upon securing a sufficient concentration in the blood, i.e., upon adequately high dosage. Furthermore, if this could be accomplished promptly in the initial attack, one might hope that the development of the damaging vascular and cardiac lesions could be forestalled.

Based on such premises, Coburn [5] has carefully studied (over a two year period) a series of cases of rheumatic fever treated with varying doses of salicylates. He attempted to gauge the activity of the infection in the absence of clinical symptoms by means of the sedimentation rate. He also devised a relatively simple method of measuring the amount of salicylate in the blood plasma as an additional control of the dosage.

In one group of 63 cases who were treated with small doses of salicylates (three to six grams a day), symptoms were relieved, but there was not a progressive fall in the sedimentation rate. These cases showed a plasma salicylate content below 250 gamma per c.c. About 40 per cent of these cases had recurrent attacks, and 21 cases developed signs of valvular disease.

[3] Coburn, A. F., and Pauli, R. H.: A precipitinogen in the serum prior to the onset of acute rheumatism, Jr. Exper. Med., 1939, lxix, 143–162.

[4] Coburn, A. F., and Kapp, E. M.: The effect of salicylates on the precipitation of antigen with antibody, Jr. Exper. Med., 1943, lxxvii, 173–184.

[5] Coburn, A. F.: Salicylate therapy in rheumatic fever. A rational technique, Bull. Johns Hopkins Hosp., 1943, lxxiii, 435–464.

In another group of cases, 10 grams of salicylate per day were administered. Those who received the drug by mouth usually became free from symptoms within 24 to 48 hours and afebrile within 72 hours. The plasma salicylate level after 24 to 48 hours ranged from about 350 to 400 gamma per c.c. If 10 grams per day were administered by intravenous infusion, these levels were reached immediately, and symptoms and fever usually subsided within 24 hours. Two cases not showing satisfactory improvement, who were given 20 grams by infusion during the second day, then showed a prompt response with a plasma salicylate level of 600 gamma per c.c. The improvement could usually be maintained by daily administration of 10 grams by mouth. The sedimentation rate in these cases fell progressively to normal within 14 days. Treatment at this level was routinely continued for two weeks longer, and was then interrupted. Two cases showed a recrudescence which was promptly controlled by resumption of treatment. None of the 38 cases receiving 10 grams of salicylate per day developed signs of valvular disease during the period of observation, although a number showed electrocardiographic abnormalities at the onset of treatment.

According to Coburn, the only toxic symptom ordinarily observed, even with maximal doses, was a "mild tinnitus." One case, however, after 10 days' satisfactory treatment abruptly developed alarming symptoms of intoxication (fever, psychosis, cutaneous eruption), and the drug had to be permanently stopped. These symptoms subsided within three days, but two days later there was a severe recrudescence of rheumatic fever with a rapid rise in the sedimentation rate.

On the basis of these observations Coburn has proposed a method for administering salicylate effectively, for the details of which the reader is referred to his article. He stresses the importance of early treatment, of securing promptly an effective concentration of salicylate in the plasma and maintaining this until the activity of the infection has subsided, using intravenous infusions if necessary, and of controlling treatment by determinations of the sedimentation rate rather than by the clinical symptoms. He emphasizes the point that smaller doses may relieve symptoms while masking a progressive inflammatory process in the tissues.

If Coburn's observations and conclusions are correct, their great importance is obvious. Many clinicians in the past have advocated the use of large doses of salicylates (10 to 12 grams a day) in rheumatic fever. Few, however, have probably appreciated the need of continuing these doses for such a protracted period after all clinical manifestations of illness have subsided. From the standpoint of practical therapeutics this point together with more adequate methods of controlling treatment constitute Coburn's major contribution. Those who have had experience with the administration of large doses of salicylate may well doubt whether the incidence of toxic symptoms will continue to be as low in a larger series of cases. Coburn's work manifestly requires confirmation in other clinics where treatment can be

adequately controlled and critically judged. A much more protracted period of observation is also necessary for its evaluation. In view of the importance of the subject, such studies will undoubtedly be forthcoming. The practical value of this therapeutic procedure is obviously independent of the validity of the hypothesis as to the mechanism by which the effect of salicylate is brought about.

Coburn recognizes the fundamental defect of salicylate, that it does not destroy the infectious agent of rheumatic fever. Until some means of doing this is discovered, however, any measure which will limit the devastation that it causes will be valuable.

REVIEWS

Technic of Electrotherapy and Its Physical and Physiological Basis. By S. L. Osborne, Assistant Professor, Department of Physical Therapy, Northwestern Medical School, and H. J. Holmquest, Lecturer in Applied Physics at the same institution, Research Engineer for General Electric X-ray Corporation. 780 pages; 23.5 × 15 cm. 1944. Charles C. Thomas, Springfield, Illinois. Price, $7.50.

The material of this book, the most noteworthy peak of electrotherapeutic bibliography in a decade, based on the authors' 16 years experience in teaching physicians, technicians, and medical students at Northwestern, falls in four categories: (1) Direct current; (2) Electrical muscle stimulation; (3) Radiation, thermogenic, and U.V.R.; (4) High frequency, (*a*) conventional, (*b*) shortwave, (*c*) surgical, (*d*) fever therapy. Each has its respective chart of indications and technic.

As a self instruction guide to the why as well as how and what of electrotherapy to those with a good grounding in science and to those whose scientific training is limited, an accompanying handbook of graded electrophysics or an ample glossary of terms, such as radan, ketone, farad, dynes, Debye units, microerg, etc., would be extremely helpful. Nomenclature of electrotherapy is clarified. Emphasis is given to rulings of the Council on Physical Therapy.

The Direct Current chapter opens with rules for a written prescription, a feature emphasized throughout. These have, within limits, an elasticity for which a technician is grateful.

There is a thorough discussion of ionizations with a table of substances used with polarity for each indicated. Copper ionization for fungus infections to hands and feet is given in detail. From the table in the Handbook of Physics and Chemistry, the electrochemical equivalents of metals most frequently employed in ion transfer are given, and in this instance, the milligrams of copper liberated are worked out:

30 minutes = .5 hour
15 minutes = .015 ampere
0.5 hour × .015 ampere = .0075 amperes hours
.0075 × 1.119 (electrochemical grams per ampere hour) = .008925 or 8.9 milligrams

The chapter on muscle stimulation reviews the recent physiology and applies the necessary procedures. The summary is quoted in full:

"The types of current fully adequate and most desirable in clinical practice for the electrical stimulation of muscle are in our opinion:

"A. The surging interrupted D.C. with Alternate Polarity, having a surge frequency of 5–100 per minute and being interrupted from 40–100 times per second (ratio periods of surge to rest are further described as being 2–1).

"B. The surging uninterrupted D.C. with Alternate Polarity having a surge frequency of 5–20 per minute."

Two chapters follow covering apparatus, early and recent, and technics.

Radiation starts with definitions of wave lengths and their respective placements in the spectrum. "The entire known electromagnetic spectrum extends from 30,000 meters to less than .01 angstrom unit in wave length—a range covering 60 octaves, only one of which, namely from 4,000—8,000 angstrom units, excites the sensation of vision. If a scale one foot long were to represent the visible spectrum, a linear scale

approximately 15 million miles long would be required to represent the 60 octaves of known radiation. Life on this planet evolved and developed in this complex radiation environment. Modification of it has marked biologic effects on both plants and animals. Radiation properly used provides a potent therapeutic and disease preventing agency. The radiations with which this discussion is primarily concerned are the infrared and the U.V.R. lying respectively in the spectral ranges 8,000–150,000 A.U. and 2,000 to 3,000 A.U."

The physics of refraction are discussed with mathematical detail.

Defining thermogenic radiation as heat producing radiation, it includes and replaces the terms phototherapy, radiant heat therapy, infrared therapy, and, to quote, "the vague misnomer deep therapy." Bodily effects are subdivided with appropriate discussions.

Ultra violet radiation is ably discussed. The chapter on artificial sources, hot body radiators, electric arcs, and glow discharges, concludes with a caption from the Council of Physical Therapy. "The fact that the erethemogenic efficiency of a source is high is not necessarily a criterion of its suitability for therapeutic purposes." For information on specific apparatus, the student is referred to the booklet *Apparatus Accepted* by the Council on Physical Therapy.

Four hundred and twenty-nine pages, over half the book, deal with high frequency currents. Over half of these pages cover the technic of local applications and fever therapy. This is perhaps a criterion of its importance to the authors.

Before considering alternating currents of high frequency, there is a brief study of alternating current circuit theory in general. Modifications of Ohm's Law as applied from D.C. currents to alternating currents, through different types of basic circuit elements, such as condensers, coils, and pure resistance, also the influence on the opposition these basic circuit elements oppose to the flow of A.C. This brings one to a consideration of inductance, inductance reactance, capacitance, admittance, susceptance resonance, current lags, with exact definitions, applied electrical laws, and problems with definite mathematical formulae.

The above principles are applied to the alternating currents of conventional diathermy and later to the diode and triode thermionic tubes with their electric and magnetic fields. Criticism is made of the term short wave diathermy. "It was undoubtedly suggested by the fact that relatively short radio waves are radiated into space from the high frequency current flowing in the currents of an oscillator. The term is somewhat misleading since it suggests that a patient is treated by a radiation field, whereas the fact is that the patient is definitely made part of a high frequency circuit, coupled relatively closely to the tank circuit of an oscillator."

The induction method of application is favored in technic of application. Briefly, the reasons given on p. 485 are:

1. The induction field generates heat in an electrolyte in direct proportion to its conductivity. Heat is dominately produced thereby in the vascular type of tissue.
2. It is in the vascular tissues that the body normally produces heat.
3. It is through the agency of the blood stream that the living body combats infection, relieves congestion, brings about elimination and repair.
4. Induction currents applied to vascular tissue best aid the body to do its work.
5. The use of the induction field is indicated in all conditions benefited by the production of an active hyperemia.

On p. 490, No. 8, the use of high frequencies of any sort to patients in metal beds is frowned upon, "Should the use be unavoidable, special precautions should be taken." Out of 40 pictures dealing with the application of induction currents, 15 are evidently in modern metal hospital beds, and there is no mention of precautions hav-

ing been taken. This occurrence in such an important book is one of the small things prolonging confusion of thought and technic about treatment.

Greater adaptability of treatment to pathology is recommended. "For certain pathologies, short treatments given at intervals throughout the day may be indicated, while for other pathologies, long periods of low intensity treatment may be more effective." Speaking of orificial electrodes, the authors express themselves in italics: *"In our opinion, generalized pelvic heating is just as effective and probably preferable for the treatment of vaginal, rectal, and prostatic conditions."* It is pointed out that condenser pad applicators are unacceptable to the Council on Physical Therapy as they are incapable of permitting a final temperature of 103°–104° F. in the deep muscles of the thigh at the end of a twenty minute application. Cuffs are acceptable to the Council for extremities only. Electrosurgery is simplified by numerous references to the book by Kelly and Ward, Saunders Company, Philadelphia—London, 1932.

Modern experimentation is discussed at length with direction implied to future investigations. The more than hundred pages on fever therapy cover at length bodily effects with emphasis on effects on blood.

From its suggested definite but elastic prescriptions, to its backbone of scientific rationale, this is the most thought provoking book on electrotherapy that has yet appeared, an adequate reflection undoubtedly to the valuable research being done at Northwestern.

G. E. S.

A Manual of Physical Therapy. Third Edition, Thoroughly Revised. By RICHARD KOVÁCS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School. 309 pages; 20.5 × 14 cm. 1944. Lea and Febiger, Philadelphia. Price, $3.25.

In his preface the author states, "a concise manual on physical therapy should serve as a welcome aid in elementary courses on this subject as well as for physicians and medical personnel seeking information on essential facts." The book fulfills the author's design aptly.

The packing of much information in small compass is illustrated by the following paragraph, one of three, on physiological effects of hyperthermy: "The pulse-rate increases in proportion to from 5–9 beats per minute to each degree Fahrenheit. The respiration also increases at a rate of about 2–12 per minute to an increase of 1° F. At a temperature of about 105° F. it is about 25 to 30 per minute. The blood pressure at first undergoes a slight elevation of systolic pressure, then declines. The diastolic pressure falls, as a rule, as soon as the temperature begins to rise, and its usual range is from 60–50 mm. in contrast to 120–80 mm. for the systolic. The basal metabolic rate increases at a rate of about 7% for each degree rise in temperature. Every person, who has undergone five hours or more of fever therapy, will lose from four to five pounds of weight due to the fluid excreted by perspiration. The kidney secretion is increased at first—later there is evidence of concentration of urine. The loss of chlorides through perspiration may amount to 2.6 grams in one febrile session. All these changes return to normal after a few hours."

The physics of thermionic and amplifier tubes are diagrammed clearly, rivalling the text. The chapter on galvanism ends with exactly noted polarity use in technics of iontophoresis for each drug named. The newer machines, combining motor wave mechanism with rectifying tube is shown (Courtesy MacIntosh Company). "Thermionic types of low frequency generators have come into use in recent years. They utilize vacuum tubes for rectifying the alternating currents and 'grid glow' tubes to rhythmically change its strength without any sort of rotating mechanism; other

thermionic devices serve to interrupt its flow." The advantage of these generators is their lower cost and absence of moving parts, with silent operation and no need of lubrication (figure 59, Courtesy Wappler, Inc.).

The basic physics of vacuum tube apparatus is an agreeably plain first lesson. The Hemingway chart of an oscillator tube mechanism is on page 153 (Courtesy Archives of Physical Therapy), and the tube itself on page 154 (Courtesy Westinghouse).

A chapter on baths illustrates full galvanic and partial galvanic and ends with a discussion on hypothermy, in both anesthetic and peripheral vascular conditions. The commending baton of the author falls heavily on the latter.

Dr. Madge C. L. McGuinness contributes a valuably suggestive chapter on exercise. She stresses the three R's—Rest, Relaxation, and Recreation, never more necessary nationally than today. Exercises for spastics and hemiplegias, in our opinion, should be based entirely on the stretch reflex concept so ably developed in exercises for this group by Dr. Phelps. If that concept is not at the base of exercise plans, exercise for this group too often does harm to body and personality.

The author concludes with a chapter on physical therapy in institutional practice. Training, departmental plans, and records share emphasis.

There is no bibliography. References are scattered through the text.

To start any beginner on the right road, the book is painstakingly clear.

G. E. S.

Physical Medicine in General Practice. By WILLIAM BIERMAN, M.D., Mount Sinai Hospital and N.Y.U. Medical College, N.Y. 654 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $7.50.

This is a general easily readable guide to physical medicine. Stress goes on pathologies, which take a full third of the book, and clinical measures of their treatment.

Climatotherapy and Spa Therapy form a chapter discussion early in the book. Numerous American spas are individualized by name and quality. The chapter and its ample index should stimulate development of the home field, as it were, in this too little developed therapy.

The author reviews some of his experiments in visible and infrared therapy. He finds the near infrared decidedly more effective in raising subcutaneous temperature than those lamps mainly infrared. The heating source in the experiments was a 260 watt carbon filament lamp held 18 inches from skin surface. Preferred dosage is optimum, not maximum. Obviously the optimum varies with varying factors in individual cases.

The conventional form of diathermy with the making of usual and unusual electrodes as vaginal electrodes from human plaster casts, and facial masks of plaster, lined with tinfoil, for the individual face, form the newer part of that topic. A warning not to discard the simple forms of heat with conventional diathermy for short wave diathermy indicates that, to this author, each has its own place. Short wave diathermy is spoken of as short wave therapy. A lucid easily understandable exposition is followed by specific technics, dosage determination, duration, frequency, preparation of patient, and precautionary measures with contraindications.

The history of fever therapy is outlined. Apparatus is discussed in detail. The author emphasizes the careful choice of the fever therapy technician. "A good technician, even though she works with relatively poor apparatus, is far better than a poor technician with the best type of apparatus." He emphasizes adequate and exact preparation of the patient for the day before and for the therapy day itself. Morphine and seconal are sedatives of choice, preferably combined. "It should be

borne in mind that morphine and the barbiturates may so disturb the control of the heat centers that a further rise in body temperature follows their administration. At 101° or 102° this may not be important but it obviously becomes a matter of vital importance if this sudden elevation occurs when the patient's temperature has reached 106° or 106.5°. The temperature should first be lowered a degree or two." Later, when intravenous administration seems desirable, we give 1000 c.c. of physiologic salt containing 5% sugar. Again, in the more serious type of cyanosis, it may be necessary to terminate the treatment abruptly; to reduce the temperature of the body as quickly as possible, and to give carbon dioxide and oxygen inhalations with salt solution intravenously. Undoubtedly due to these and other careful precautions similarly outlined, the author can state, "In my own experience, embracing several thousand treatments, there has been but one death."

The pathological changes leading to death during fever therapy form an exact and interesting discussion.

Indications for electrosurgery with its disadvantages are tabled on pages 214 and 215.

Iontophoresis rates a full discussion as does galvanic technic. Electrolysis is given in full. Electrodiagnosis amplified with splendidly drawn charts (not signed), chronaxies, and their significance, are discussed. "The Schnee bath is sometimes used to induce movement of the muscles of the extremities en masse." "Spas abroad use the general galvanic treatment in full length tubs at 95° with electrodes out of the patient's reach, and the tub grounded." Indications and contraindications are fully outlined.

Metabolic changes form an important section of the chapter on ultra-violet radiation with the notation that while overdosage of Vitamin D may result from excess oral medication it does not occur from an overexposure to photochemical radiation, also that "radiation is ineffective in the presence of dietary deficiency of calcium and phosphorus." Ultra violet radiation of the blood in cases of peritonitis, puerperal sepsis, post-abortional sepsis, bacteremia or toxemia is recommended as a safe procedure following the technic developed by E. K. Knott of Seattle. The blood is drawn from a vein in the arm, citrated, drawn from the container by a pump and intensely irradiated by a water-cooled quartz mercury lamp. The author's more simple technic follows: "the removal of about 5–8 c.c. of blood which is citrated, irradiated with a mercury vapor lamp and then injected intramuscularly. Injections are repeated two or three times a week for from fourteen or eighteen times. This method is proposed for the relief of pain in arthritis and in chronic muscular rheumatism, or in the treatment of acute allergic diseases of the skin. This is really a form of protein therapy."

Massage, exercise and occupational therapy detailed, fill out the physical medicine scheme.

The sketches on exercise surprise one. They do not follow in all instances good exercise technic. Figures 191 and 205 are notable offenders. Foot extensors in the series seem needlessly put to a strain, while exercise of another part is being performed. This is a regrettable occurrence in a new book by an outstanding author.

Conduct of Treatments forms a short valuable chapter. Written prescriptions are desirable. Hibben says, "that when a department is in charge of a physician trained in physical medicine and when his assistants are registered P.T. technicians, the medico legal liability of the hospital is diminished about 90%." This point has connotations to medical students in doubt about a specialty. The paragraphs on departmental accidents rate study, not only by technicians and physicians, but by hospital administrators, as does the appendix giving required hospital specifications of apparatus for the City of New York. Council approval is obvious but not stated.

G. E. S.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Simplified Diabetic Management. 4th Edition. By J. T. BEARDWOOD, JR., A.B., M.D., F.A.C.P., and H. T. KELLY, M.D., A.A.C.P. 172 pages; 19.5 × 13.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $1.50.

Leukopenia and Agranulocytosis. By WILLIAM DAMESHEK, M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). (Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work.) 78 pages; 24 × 16 cm. 1944. Oxford University Press; New York City. Price, $1.75.

The Gastro-Intestinal Tract. A Handbook of Roentgen Diagnosis. By FRED JENNER HODGES, B.S., M.D. 320 pages; 21 × 14.5 cm. 1944. Year Book Publishers, Inc., Chicago. Price, $5.50.

Surgical Disorders of the Chest. Diagnosis and Treatment. By J. K. DONALDSON, M.D., F.A.C.S. 364 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia. Price, $6.50.

The Practice of Medicine. Fourth Edition. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D. 1444 pages; 26 × 18 cm. 1944. C. V. Mosby Company, St. Louis. Price, $10.00.

Fundamentals of Internal Medicine. Second Edition. By WALLACE MASON YATER, A.B., M.D., M.S. in (Med.), F.A.C.P. 1204 pages; 25 × 17.5 cm. 1944. D. Appleton-Century Co., New York City. Price, $10.00.

The Art of Anaesthesia. Seventh Edition. By PALUEL J. FLAGG, M.D. 519 pages; 23.5 × 16.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $6.00.

X-Ray Examination of the Stomach. By FREDERIC E. TEMPLETON, M.D. 516 pages; 23.5 × 16 cm. 1944. University of Chicago Press, Chicago. Price, $10.00.

Manual of Psychological Medicine. By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S.E. 298 pages; 22 × 14.5 cm. 1944. Williams & Wilkins Company, Baltimore. Price, $5.00.

A New German-English Psycho-Analytical Vocabulary. By ALIX STRACHEY. 84 pages; 22 × 14.5 cm. 1943. Williams & Wilkins Company, Baltimore. Price, $2.50. (Research Supplements to the International Journal of Psycho-Analysis. Edited by Edward Glover. No. 1.)

Keys to the Mosquitoes of the Australasian Region, Including a Synopsis of Their Distribution and Breeding Habits. By KENNETH L. KNIGHT, Lieut., H–V(S), USNR, RICHARD M. BOHART, Lieut.(jg), H–V(S), USNR, and GEORGE E. BOHART, Lieut., H–V(S), USNR—U. S. Naval Medical Research Unit No. 2. 71 pages; 28 × 22 cm. 1944. National Research Council—Division of Medical Sciences. Issued by the Office of Medical Information (under grant of Johnson & Johnson Research Foundation).

Antimalarial Drugs. General Outline. By OWSEI TEMKIN, M.D., and ELIZABETH M. RAMSEY, M.D. 128 pages; 28 × 22 cm. 1944. National Research Council

—Division of Medical Sciences. Issued by the Office of Medical Information (under grants of the Carnegie Corporation and the Johnson & Johnson Research Foundation).

Spontaneous Pneumothorax. By JAMES J. WARING, M.D. 34 pages; 28 × 22 cm. 1944. National Research Council—Division of Medical Sciences. Issued by the Office of Medical Information (under grant of the Johnson & Johnson Research Foundation).

The Blood Plasma Program. By JAMES A. PHALEN, M.D., Colonel, U. S. Army. 67 pages; 28 × 22 cm. 1944. National Research Council—Division of Medical Sciences. Issued by the Office of Medical Information (under grants of the Carnegie Corporation and the Johnson & Johnson Research Foundation).

COLLEGE NEWS NOTES

A. C. P. Members in the Armed Forces

Dr. John S. Staneslow, F.A.C.P., Waterbury, Conn., recently entered the armed forces of the United States. 1,715 Fellows or Associates of the College have been commissioned during the present war; many others have volunteered but were not accepted for various reasons.

Several members have been honorably discharged from active duty, including the following:

Lt. Col. Dwight Lawson, (MC), USA—June 30, 1944
Brigadier Jonathan C. Meakins, RCAMC—September 7, 1944
Captain E. David Sherman, RCAMC—June 10, 1944
Lt. Comdr. Warren F. Kahle, (MC), USNR—July 1, 1944
Captain Elmer E. Kottke, (MC), AUS

New Life Member

Dr. Harold S. Davidson, F.A.C.P., Atlantic City, N. J., became a Life Member of the College on September 13, 1944.

Gifts to the College Library

The following gifts are gratefully acknowledged:

Books

Dr. Harry L. Arnold, Sr., F.A.C.P., Honolulu, T. H.—"Poisonous Plants of Hawaii."
Dr. T. Lyle Hazlett, F.A.C.P., East Pittsburgh, Pa.—"Introduction to Industrial Medicine."

Reprints

Dr. John J. Andujar, F.A.C.P., Fort Worth, Tex.—1 reprint.
Dr. George E. Baker, F.A.C.P., Casper, Wyo.—4 reprints.
Joseph L. Holland (Associate) Captain, (MC), AUS—1 reprint.
A. M. Hutter, F.A.C.P., Lieutenant Commander, (MC), USNR—1 reprint.
Morrill L. Ilsley, F.A.C.P., Claremont, Calif.—1 reprint.
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—1 reprint.
Dr. Samuel G. Shepherd, F.A.C.P., Philadelphia, Pa.—2 reprints.
Paul S. Strong (Associate), Captain, (MC), AUS—1 reprint.
Dr. Howard Wakefield, F.A.C.P., Chicago, Ill.—1 reprint.
Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—2 reprints.

A.C.P. Board of Regents Will Meet December 16

The regular autumn meeting of the Board of Regents of the College will be held at the College Headquarters in Philadelphia, December 16, 1944. On the preceding day, December 15, there will be held in Philadelphia a Regional Meeting of the College for Eastern Pennsylvania, New Jersey and Delaware. Also, the various Committees of the College will meet and prepare their reports, December 15.

Deadline for Proposal of Candidates

Proposals of candidates for Associateship or Fellowship for review by the Committee on Credentials on December 15, and final action by the Board of Regents on December 16, must be filed with the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa., at least thirty days in advance thereof, or by November 15, 1944.

Vancouver Regional Meeting of the College

A Regional Meeting of the American College of Physicians and a War-Time Graduate Medical Meeting was held at the Hotel Vancouver, Vancouver, B. C., September 14–15, for the territory embracing Idaho, Oregon, Washington, Alberta, British Columbia, Manitoba and Saskatchewan. Dr. George F. Strong, Regent of the College, of Vancouver, was the General Chairman and the Governors of the participating States and Provinces constituted the Executive Committee.

The program was as follows:

Thursday, September 14

Morning Session

Presiding

T. Homer Coffen, F.A.C.P.

Regent, Portland, Oregon

"The Recent Status of Rickettsia Disease." Dr. Matthew Riddle, Associate Professor of Medicine, University of Oregon Medical School.

"Control of Staphylococcic Infections with Sulfonamide Drugs." Lieut. Col. Roy H. Turner, Chief of the Communicable Disease Treatment Branch, Army Service Forces, Washington, D. C.

"Clinical Experience with Penicillin." Capt. Chas. E. Watts, F.A.C.P., Medical Officer in Command, United States Naval Hospital, Seattle, Wash.

"Some Pharmacological Problems in the Use of Chemotherapeutic Drugs." Dr. Norman D. Davis, Professor of Pharmacology, University of Oregon Medical School.

Luncheon

Presiding

J. W. Scott, F.A.C.P.

Governor, Edmonton, Alberta

Speaker

Maj. Gen. G. R. Pearkes, V.C., C.B., D.S.O., M.C. G.O.C. in C. Pacific Command

Afternoon Session

Presiding

E. G. Bannick, F.A.C.P.

Governor, Seattle, Washington

"Respiratory Limitations in Altitude Flying." Group Capt. G. E. Hall, Consultant in Medicine, R.C.A.F., Ottawa, Ontario.

"Respiratory Disease Problems in an East Coast Base." Surgeon-Comdr. J. Wendell MacLeod, Consultant in Medicine, R.C.N.V.R., Halifax, N.S.

"Visualization of the Chambers of the Heart and Great Vessels." Lieut. Comdr. Israel Steinberg, M.C.-V's, U.S.N.R., F.A.C.P.

"Experimental and Clinical Aspects of Carotid Sinus Reflexes." Dr. Hance Haney, Professor of Physiology, University of Oregon Medical School.

Dinner

7:00 P.M.

Presiding

G. F. STRONG, F.A.C.P

Regent, Vancouver, B. C.

Speakers

DAVID P. BARR, F.A.C.P.

President-elect American College of Physicians
New York City

COMMANDER CORYDON M. WASSELL (M.C.)
U.S.N.R.

FRIDAY, SEPTEMBER 15

Morning Session

Presiding

G. M. POINDEXTER, F.A.C.P.
Governor, Boise, Idaho

"Hepatitis." Lieut. Col. Roy H. Turner, Chief of the Communicable Disease Treatment Branch, Army Service Forces, Washington, D. C.

"Psychosomatic Medicine." Brig. W. P. Warner, Deputy Director General of Medical Services, Ottawa, Ontario.

"Gastroenterological Problems in the Canadian Navy." Surgeon-Comdr. J. Wendell MacLeod, Consultant in Medicine, R.C.N.V.R., Halifax, N.S.

"Some Principles and Problems in Immunity." Dr. C. E. Dolman, Head of Department of Bacteriology and Preventive Medicine, University of British Columbia, and Director of Provincial Laboratories.

"Thiouracil in Graves' Disease." Dr. David P. Barr, F.A.C.P., Professor of Medicine, Cornell University Medical College, New York City.

Afternoon Session

Presiding

HOMER P. RUSH, F.A.C.P.

Governor, Portland, Oregon

"Body Section Radiography." Comdr. Wendell G. Scott, M.C.-V.'s U.S.N.R.

"Maintenance of Normal Body Temperature in Service Personnel." Group Capt. G. E. Hall, Consultant in Medicine, R.C.A.F., Ottawa.

"Some Experience with the Use of Gold Salts in the Treatment of Arthritis." Dr. P. H. Sprague, F.A.C.P., Assistant Professor of Clinical Medicine, University of Alberta.

"Observations on Active Rheumatic States." Dr. John MacEachern, F.A.C.P., Assistant Professor of Medicine, University of Manitoba.

"Malaria Control"—with two films. Lt. Commander Frank P. Mathews, Malaria Indoctrination Officer, 13th Naval District, Seattle, Wash.

American College of Surgeons Cancels 1944 Clinical Congress

By action of its Board of Regents, the American College of Surgeons has cancelled its Annual Clinical Congress for 1944 because of the acute war situation, involving greater demands than at any time in the past upon our transportation for the carrying of wounded military personnel, troops and war materiel. The Congress was to have been held in Chicago, October 24–27.

Aid to Libraries in War Areas

Up to the end of 1943, $160,873.62 has been spent for subscriptions to 325 scholarly and scientific journals, to be stored in this country, for distribution after the war to libraries in war areas. Funds were provided by grant by the Rockefeller Foundation, which has allotted from $50,000 to $70,000 annually for this purpose, since 1941. The fund is administered by the Committee on Aid to Libraries in War Areas of the American Library Association. The Annals of Internal Medicine is one of the medical journals for which a number of subscriptions have been placed and several volumes of past issues since the outbreak of the war are being stored for later shipment. These volumes have been supplied at cost.

The New York Institute of Clinical Oral Pathology

The first open meeting of the New York Institute of Clinical Oral Pathology will take place in Hosack Hall at the New York Academy of Medicine, New York City, October 30, 1944, at 8:15 p.m., the program to be devoted to a symposium on "Fluorine in Dental Public Health."

News from the Office of the Surgeon General, U. S. Army

The post of Assistant Surgeon General, to be filled by Brigadier General Raymond W. Bliss, has been created in a partial reorganization of the Surgeon General's Office. The Assistant Surgeon General will act for the Surgeon General in coördinating the work of the Operations Service, the various professional divisions, the Military Personnel Division and the activities of other divisions and services that affect operations.

A new Professional Administrative Service is created, with Colonel Arden Freer, F.A.C.P., as Chief and Colonel E. R. Long, Deputy Chief. It will include the following: Physical Standards Division, Nursing Division, Medical Statistics Division, Professional Inquiries Unit, Women's Health and Welfare Unit.

Major General George F. Lull, F.A.C.P., a member of the Committee on Physical Fitness of the American Medical Association, attended the Joint Committee on

Physical Fitness at Chicago, August 28. This conference represents the Army, Navy and civilian groups. The Committee on Physical Fitness was established by presidential order on April 29, 1943, to: (1) define and study problems relating to the promotion of physical fitness, in coöperation with national agencies and organizations, and encourage the development of coöperative programs for their solution; (2) serve as a center for the stimulation of State, district, and local programs for the promotion of physical fitness; (3) make available to States, localities, and organizations and agencies, upon request, the services of specialists in physical fitness; (4) prepare materials and serve as a clearing house on informational matters pertaining to the development of a national program of physical fitness.

Colonel James E. Ash, F.A.C.P., former curator of the Army Medical Museum, returned to his work July 25, after an extensive absence, during which he toured the North African theater of operation and sustained an eye injury which necessitated his evacuation to the Walter Reed General Hospital in Washington. His trip was taken to inspect the activities of the museum and Medical Arts Services which is collecting material for research and training in tropical diseases. The Museum is undertaking to supply all medical schools in the United States and Canada with material.

Colonel Ash now holds the appointment of Director of the Army Institute of Pathology, Army Medical Museum. This institute will serve as a central laboratory in pathology for all Army hospitals, including those in the theaters of operations. The material collected is available for research, teaching and historical purposes.

The Surgeon General's Office is seeking qualified men to become commissioned officers in the Sanitary Corps, and has announced the minimum requirements of enlisted personnel for appointment as second lieutenants. Applicants must have a bachelor's degree with an appropriate science major, and a minimum of two years experience in the particular field in which the applicant is qualified.

"Global Epidemiology," Volume 1 of a series on the geography of disease and sanitation covering particularly India, the Far East and the Pacific Area, will be published shortly. Brigadier General J. S. Simmons, F.A.C.P., Chief of the Preventive Medicine Service, Office of the Surgeon General, is one of the authors.

The Army Nurse Corps

The Army Nurse Corps, in conjunction with the Office of War Information, the Red Cross, the National Nursing Council for War Service, the War Manpower Commission, and the Recruiting Publicity Bureau of the Army, is making a concentrated effort to obtain 4,000 nurses by October. The need is urgent because of the increasing number of casualties.

A special treatment center for malaria and other tropical diseases has been opened at the Moore General Hospital, Swannanoa, N. C., by the Army Medical Department. It is under the command of Lt. Col. Joseph M. Hayman, F.A.C.P., of Cleveland, who has spent two years in the South Pacific studying tropical diseases. Lt. Col. Francis R. Dieuaide, F.A.C.P., Chief of the Tropical Disease Branch, Medical Division of the Surgeon General's Office, will administer the scientific phases of its activities.

Attendance of Medical Corps Officers at Medical Meetings

Under date of February 24, 1941, the Adjutant General issued the following to all Army, Army Corps and Corps Area Commanders:

"You are authorized to permit officers of the Medical Corps under your jurisdiction who desire to attend meetings of any National Societies to do so on a detached service status and without expense to the Government, provided their services can be spared."

The Whole Blood Program of the Surgeon General

The first shipment of whole blood from the United States to soldiers wounded in France was made by the U. S. Army Medical Department by Army plane on August 21. Daily shipments have been made since—250 pints a day the first week, 500 pints a day the second week and 750 pints a day is the goal. Type "O" blood is being collected by the Red Cross for the shipments. The whole blood is prepared on the day it is drawn and 24 hours after it leaves the United States, it is available for transfusion in France.

Major Leon H. Warren, F.A.C.P., Chief of Research Coördination Branch, Technical Division, since February 4, 1944, has been promoted recently to Lieutenant Colonel.

Dr. George E. Baker, F.A.C.P., Casper, Wyo., has been appointed Acting Secretary of the Wyoming State Medical Society. Dr. Baker has recently completed the revision of the chapter on Rocky Mountain Spotted Fever for Tice's Practice of Medicine.

Dr. J. Warrick Thomas, F.A.C.P., who has been Head of the Department of Allergy of the Cleveland Clinic, Cleveland, Ohio, since January 1, 1939, is removing to Richmond to take over the practice of the late Dr. Warren T. Vaughn, and will be associated with Dr. W. Randolph Graham, F.A.C.P., in the establishment of the Vaughn Memorial Clinic, 201 West Franklin Street, Richmond, Va. His practice will be limited to Allergy and Internal Medicine. Dr. Thomas is a member of the Board of Regents of the American College of Allergists and Assistant Editor of their journal, *Annals of Allergy*.

Dr. E. David Sherman (Associate), Sydney, Nova Scotia, was retired from the Royal Canadian Army Medical Corps on June 10, 1944. He spent some time in postgraduate work in New York and Philadelphia and has now resumed practice at 327 Charlotte Street, Sydney. (Ed. Note: In Canada a retired officer is given an extra month's pay and extended the privilege of wearing his uniform.)

Dr. Jonathan C. Meakins, F.A.C.P., has retired September 7 from active service as Brigadier in the Royal Canadian Army and has resumed his work as Dean of McGill University Faculty of Medicine at Montreal.

Dr. Robinson Bosworth, F.A.C.P., Superintendent and Medical Director, Pleasant View Sanatorium, East St. Louis, Ill., was awarded the Hoyt E. Dearholt Memorial Medal for services in tuberculosis control in the Mississippi Valley Conference territory at the annual meeting of that Conference at Chicago, May, 1944.

New A.C.P. Appointments Due to the Deaths of Dr. Charles Hartwell Cocke and Dr. William B. Breed, Members of the Credentials Committee

Two new appointments have been made until the next regular meetings of the Board of Regents and Board of Governors. Dr. Charles Fred Tenney, F.A.C.P., of New York City, will fill the vacancy caused by Dr. Cocke's death, as an appointee of the Board of Regents, and Dr. J. Edwin Wood, Jr., F.A.C.P., of the University of Virginia, will fill the vacancy caused by the death of Dr. Breed, as an appointee of the Board of Governors.

Dr. Chauncey W. Dowden, F.A.C.P., Louisville, Ky., heretofore Vice Chairman of the Board of Governors, will succeed to the chairmanship, succeeding Dr. Breed.

Dr. Reginald Fitz, Regent of the College, Boston, will attend to the ordinary duties of the College Governor for Massachusetts, including the endorsement of candidates, until a Governor to succeed Dr. Breed has been officially appointed.

Dr. George Morris Piersol, F.A.C.P., of Philadelphia, has been appointed to succeed Dr. Breed as the appointee of the American College of Physicians on the Committee on War-Time Graduate Medical Meetings.

Dr. William G. Leaman, Jr., F.A.C.P., has been made Associate Medical Chief of the Memorial Hospital, Roxborough, Pa.

Dr. William D. Stroud, F.A.C.P., is a member of the joint committe of the American Medical Association and the National Committee on Physical Fitness, referred to under news items from the Surgeon General's Office. This joint committee is under the chairmanship of Colonel Leonard G. Rowntree, (MC), AUS, F.A.C.P., Chief of the Medical Division, National Selective Service.

The Twenty-second Annual Fall Clinical Congress of the Kansas City Southwest Clinical Society was held October 2–4, 1944, at Kansas City. Among the guest speakers were Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, "The Leukemias," "Changes in the Blood Due to Various Drugs, and a Consideration of Blood Transfusion Reactions," and "The Problem of Chronic Ulcerative Colitis"; Dr. Russell Haden, F.A.C.P., Cleveland, "Treatment of Rheumatoid Arthritis" and "The Treatment of Pernicious Anemia."

Under the direction of Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, the Chicago Institute for Hospital Administrators was held at the International House, University of Chicago, September 11–22, and sponsored by the American College of Hospital Administrators. The forenoons were devoted to lectures; the afternoons to seminars and field trips to selected hospitals for demonstrations; and the evenings, to conferences on administrative and departmental problems facing hospitals.

Lt. Col. Orpheus J. Bizzozero, F.A.C.P., Chief of the Allied Military Government's Health Section, recently reported that one in every five persons in Rome has tuberculosis, a situation attributed to nine months suffering under German occupation.

Metropolitan Life Insurance Company predicts that about the year 1950, diabetes will begin to outrank tuberculosis as a cause of death in this country. While deaths from tuberculosis in this country continue to decline, deaths from diabetes are progressively increasing. In 1909, the statisticians report that tuberculosis was the leading cause of death in this country, with diabetes ranking sixteenth. At the present

time, tuberculosis ranks seventh and diabetes ninth. The growing proportion of older people in the population plus the improvement in the fight against infectious diseases explains the change in rank of deaths from diabetes and tuberculosis.

Dr. Fred B. Clarke, F.A.C.P., Long Beach, Calif., and Dr. John Severy Hibben (Associate), Pasadena, are members of a joint committee composed of three members of the Los Angeles Bar Association and three members of the Los Angeles County Medical Association, which are sponsoring a program, "The Doctor Speaks to the Attorney," consisting of a series of lectures from September to December, covering varying legal medical problems.

Dr. Frank A. Trump, F.A.C.P., Ottawa, Kansas, is a Vice President of the Kansas Tuberculosis and Health Association.

Lt. Col. Arthur Parker Hitchens, F.A.C.P., has been retired from active service in the U. S. Army, and has been appointed Health Commissioner of Wilmington, Del. He is also Professor of Public Health and Preventive Medicine at the University of Pennsylvania School of Medicine.

Dr. Arthur H. Sanford, F.A.C.P., Rochester, Minn., has been reëlected President of the American Board of Pathology. Dr. Howard T. Karsner, F.A.C.P., Cleveland, and Dr. Alvin G. Foord, F.A.C.P., Pasadena, have completed their two terms of service in the Board and have retired therefrom.

Dr. Miletus B. Jarman, F.A.C.P., Hot Springs, Va., addressed the American Congress of Physical Therapy at Cleveland, Ohio, September 6–9, on "Mineral Water Therapy; An Appraisal." Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the U. S. Army, was a guest speaker at the annual banquet.

Brigadier General Hugh J. Morgan, F.A.C.P., Director of the Medical Division, Brigadier General James S. Simmons, F.A.C.P., Chief of Preventive Medicine Service, Colonel William Paul Holbrook, F.A.C.P., representative of the Army Air Forces, and Colonel R. B. Skinner (Associate), representative of the Army Ground Forces are members of a committee appointed by the Office of the Surgeon General of the Army "to formulate plans for post-war training of medical corps officers who will be separated from the military service at the end of the war."

Dr. Emma S. Moss, F.A.C.P., New Orleans, Assistant Professor of Pathology and Bacteriology, Louisiana State University School of Medicine, has been elected Secretary-Treasurer of the Louisiana Association of Pathologists.

Dr. Francis E. Harrington, F.A.C.P., Minneapolis, will serve as the Acting Superintendent of the Minneapolis General Hospital until the appointment of a full-time Superintendent. He recently retired as Minneapolis Health Commissioner.

Dr. Theodore R. Van Dellen, F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School, is the lecturer in the medical science course in hospital administration, offered at the Northwestern University in the first semester of the current school term. There are five courses, in all, devoted to the history and development of hospitals, organization and management of hospitals, professional

services to the hospital patient, legal and political and sociological aspects of hospital administration and fundamentals of medical science.

Dr. William D. Robinson (Associate), of Vanderbilt University School of Medicine of Nashville, Tenn., has accepted an appointment as Assistant Professor in the Department of Medicine and Director of the Rackham Arthritis Research Unit of the University of Michigan Medical School, effective September 1.

Dr. Martin H. Collier, F.A.C.P., Grenloch, N. J., is President of the New Jersey State Department of Health.

Dr. Stockton Kimball, F.A.C.P., Buffalo, Associate in Medicine and Pharmacology at the University of Buffalo School of Medicine, was recently appointed Assistant Dean of the School.

The 94th Annual Session of the Medical Society of the State of Pennsylvania was held in Pittsburgh, September 19–21, under the presidency of Dr. Augustus S. Kech, F.A.C.P., Altoona.

A feature of the meeting was a panel discussion on clinical endocrinology by Dr. Charles W. Dunn, F.A.C.P., Philadelphia, Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., and Dr. Emil Novak, Baltimore.

Dr. Wingate M. Johnson, F.A.C.P., Winston-Salem, N. C., is President of the American Geriatrics Society. Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., is a Vice President.

Dr. Alvin L. Barach, F.A.C.P., New York City, addressed the Aero Medical Association at St. Louis, September 4–6, on, "Development of Pulmonary Active Tuberculosis as the Result of Aeroembolism at Simulated Altitudes above 40,000 feet."

Dr. Willard C. Rappleye, F.A.C.P., New York City, is a member of a committee headed by Dr. Arthur Bachmeyer of Chicago to make a survey of American hospitals and their post-war expansion needs. The survey will be financed by a grant of $35,000 each by the Commonwealth Fund of New York, the National Foundation for Infantile Paralysis and the W. K. Kellogg Foundation. Hope is expressed that the study will determine the adequacy of distribution of present hospital facilities and the best method for ensuring adequate hospital care to all citizens.

American Board of Internal Medicine Examinations

The next written examination of the American Board of Internal Medicine will be held February 19, 1945, in various parts of the United States. The closing date for acceptance of applications for this examination will be December 15, 1944.

War-Time Graduate Medical Meetings and Kentucky State Medical Association Meeting Combined

On September 18–20, 1944, there was a combined meeting of the War-Time Graduate Medical Meetings and the Kentucky State Medical Association at Lexington, Ky. The Regional Meeting Committee of the War-Time Graduate Medical Meetings

consisted of Dr. Elmer L. Henderson, Chairman, Dr. Chauncey W. Dowden, F.A.C.P., and Dr. H. H. Shoulders. A number of Fellows of the College, including the following, participated in the program:

Dr. John A. Toomey, Cleveland—"Chemotherapeutics in Pediatrics."
Brig. Gen. Hugh J. Morgan, Washington—"The Medical Aspects of Penicillin" in a Symposium on Chemotherapy.
Dr. William D. Stroud, Philadelphia—"Cardiovascular Diseases."
Dr. Oscar O. Miller, Louisville—(Presidential Address). "Some Aspects of the Tuberculosis Problem."
Dr. Roger I. Lee, Boston—"Accelerated Medicine Today and Tomorrow."
Brig. Gen. James S. Simmons, Washington—"The New Weapons of Control of Insect-Borne Diseases."
Dr. Ralph Pemberton, Philadelphia—"Arthritis."
Col. John D. Youmans, Washington—"Nutrition—Its Relation to Deficiency Diseases."

The Inaugural Meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia was held September 13, 1944, at which Dr. Eugene P. Pendergrass, F.A.C.P., retired as President and Dr. Charles L. Brown, F.A.C.P., was installed as President.

Dr. John T. O'Mara, F.A.C.P., Baltimore, has been reëlected Secretary-Treasurer of the Board of Medical Examiners of Maryland.

Dr. Henry Boswell, F.A.C.P., Sanatorium, Miss., has been elected Vice President of the Mississippi State Hospital Association.

Dr. Francis G. Blake, F.A.C.P., Dean and Professor of Medicine, Yale University School of Medicine, with the assistance of his staff, and Dr. Samuel C. Harvey, Professor of Surgery at Yale, and his staff, conducted an afternoon symposium on penicillin medicine and surgery during the twentieth clinical congress of the Connecticut State Medical Society at New Haven, September 28-29.

Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the U. S. Army, was the principal speaker at the commencement exercises of the 1944 class at Northwestern University Medical School, September 14.

Dr. Carl H. Gellenthien, F.A.C.P., Valmora, N. M., will act as the New Mexico editor on the editorial staff of the *Rocky Mountain Medical Journal,* which has become the official journal of the New Mexico Medical Society.

Dr. Gellenthien was recently installed as President of the New Mexico Medical Society.

Dr. Lawrence Reynolds, F.A.C.P., Detroit, delivered the Caldwell-Carman Lecture before a joint meeting of the American Roentgen Ray Society and the Radiological Society of North America at Chicago, September 26.

Drs. R. M. Craig (Associate), Dayton, George X. Schwemlein (Associate), Cincinnati, and H. W. Kendell, Dayton, reserve officers in the U. S. Public Health Service, stationed at the Chicago Intensive Treatment Center, spoke on "Physiologic

Studies and Technics Employed During Fever-Chemotherapy of Early Syphilis" at the twenty-third annual meeting of the American Congress of Physical Therapy, Cleveland, September 6.

Major Maurice J. Abrams, F.A.C.P., (MC), AUS, recently returned from twenty-four months of duty overseas, where he was Chief of the Medical Service at one of the Army Hospitals in London. He is now on limited duty as Assistant Chief of Medical Service, Station Hospital, Fort Jackson, S. C. Major Abrams was formerly in practice at Brewton, Ala.

New York Regional Meeting of the College

The American College of Physicians conducted its first Regional Meeting for the State of New York in New York City, Friday, October 20, under the General Chairmanship of Dr. Asa L. Lincoln, F.A.C.P., Governor for Eastern New York, and with the coöperation and participation of Dr. Nelson G. Russell, Sr., F.A.C.P., of Buffalo, Governor for Western New York.

In the forenoon, members of the College were the guests of the New York Academy of Medicine, in connection with its Seventeenth Graduate Fortnight, at its Exhibit, which demonstrated recent advances in the etiology, pathology, diagnosis, prophylaxis and treatment of infections. The afternoon scientific session, at which Dr. Russell presided, was held at the New York Hospital and consisted of the following presentations: Dr. George Baehr, F.A.C.P., "Penicillin Treatment of Subacute Bacterial Endocarditis due to Enterococcus"; Dr. Homer Swift, "Recent Developments in Our Knowledge of Rheumatic Fever"; Dr. William C. Von Glahn, "Rheumatic Arteritis"; Dr. Ralph Boots, F.A.C.P., "Differential Diagnosis of Rheumatic Fever"; Dr. Arthur C. DeGraff, F.A.C.P., "The Cardiac Factor in Pneumonia"; Dr. Arthur J. Patek, Jr., "Liver Disease"; Dr. Walsh McDermott, "Penicillin Treatment of Syphilis"; Dr. George Wolff, "Current Treatment of Meningococcus Meningitis"; Dr. J. Casals, "A Current View of the Rabies Problem." Cocktails and dinner were served at the Waldorf-Astoria Hotel, following which the members were again the guests of the New York Academy of Medicine at a Panel Discussion on "Evaluation of Sulfa Drugs and Penicillin," Dr. David P. Barr, F.A.C.P., Chairman, and Drs. Rene J. Dubos, Colin M. MacLeod, John F. Mahoney, Frank L. Meleney and William S. Tillett members.

Dr. Mahlon Ashford, F.A.C.P., was Chairman of the Program Committee and Dr. Charles F. Tenney, F.A.C.P., was Chairman of the Committee on Arrangements.

Dr. R. H. Kampmeier, F.A.C.P., Nashville, has been appointed Acting Director of the Department of Medicine at Vanderbilt University School of Medicine.

Oak Leaf Cluster, Distinguished Service Medal, Awarded Brigadier General Edgar Erskine Hume

Brigadier General Edgar Erskine Hume, F.A.C.P., has been awarded the Oak Leaf Cluster to the Distinguished Service Medal in recognition of service as Chief of the Allied Military Government Section, Fifth Army, in Italy, his citation reading, in part: ". . . he successfully carried out one of the most extensive military government tasks ever accomplished by the United States, being charged with the government of Campania, a region of 6,000,000 inhabitants including Naples, one of Italy's largest cities. He made detailed plans for the administration of Naples, which, under his orders, were put into immediate execution when the city was taken on Oct. 1, 1943.

"Despite enormous handicaps in Naples, where the Germans had destroyed the water supply, electric power sources, drains and other public utilities, had mined buildings, despoiled hospitals, dispersed the police and in general paralyzed the civil administration, he was able by his unusual ability and devotion to duty to restore order forthwith and within a few weeks to return the city's functions almost to normal. A threatened epidemic of typhoid was averted by his wise preventive measures. Our victory was thus hastened, as the army commander was free to perform purely military functions without the added burden of civil government.

"The respect in which this officer was held by the Italians, his intimate knowledge of the country, its people and language, and his rare administrative skill and leadership made him unique in his efficient handling of an extremely difficult and politically delicate task."

General Hume received the Distinguished Service Medal during World War I as Commissioner of the American Red Cross after the war in Serbia. He holds many academic degrees from American and foreign institutions and several decorations from foreign governments. He graduated from Johns Hopkins University School of Medicine in 1913, and has been a Fellow of the American College of Physicians since 1926.

Dr. Christopher G. Parnall, F.A.C.P., recently celebrated his twentieth anniversary as Medical Director of the Rochester General Hospital, Rochester, N. Y.

War-Time Graduate Medical Meetings

Region No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole.

Mayo General Hospital, Galesburg, Illinois

October 18 — High Blood Pressure
- *a.* Pathological—Physiological Basis—Conservative Therapy—Renal Extracts
- *b.* The Surgical Treatment

November 1 — Laboratory Diagnosis—and its relationship to treatment
- *a.* Hypoproteinemia—Alkalosis—Acidosis—Dehydration—Electrolytic Balance

November 15 — Conditions Affecting Glucose Metabolism
- *a.* Endocrine—Pituitary—Thyroid—Adrenal—Pancreatic
- *b.* Renal, Alimentary, Hepatic. Diff. Diagnosis and Treatment

Camp Ellis, Illinois

October 18 — Diseases of the Intestinal Tract
- *a.* Regional Ileitis, Colitis, Diverticulitis. Diagnosis and Treatment
- *b.* Dysentery—Army and Bacillary
- *c.* Malignancies

November 1 — Symposium on Organic Neurology
- *a.* Central and Peripheral

November 15 — Dermatological Diseases
- Clinic with Presentation of Cases and Slides. Diagnosis and Treatment.
- *a.* The Less Common Venereal Diseases
  - Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid, Yaws—Slides—Diagnosis and Treatment

Camp Grant, Illinois

October 18 Malignancies in the Army Age Group
- *a.* Melanomata
- *b.* Teratomata
- *c.* Lymphoblastomata

November 1 Endocrinology
- *a.* Addison's Disease, Adrenal Cortex in Shock, Parathyroid Tetany, Traumatic Hypogonadism, Hypothyroidism, Hyperthyroidism, Post Traumatic Pituitary Syndrosis

November 15 Virus and Rickettsial Diseases
- *a.* Virus Diseases
- *b.* Rickettsial Diseases

Chanute Field, Rantoul, Illinois

October 18 Thrombosis, Thrombophlebitis and Anticoagulants
- *a.* Thrombosis, Thrombophlebitis and Embolism—Diagnosis and Treatment
- *b.* Heparin and Dicoumarol
  Action and Therapeutic Use

November 1 Chronic Chest Diseases and Disease of the Larynx
- *a.* Tuberculosis, Pneumonoconiosis, Chronic Bronchitis, Bronchiectasis, Cysts, Fungus Infections, etc.
- *b.* Neoplasm—X-Ray and Surgical Treatment—Coccidioidomycosis and Allied Conditions
- *c.* Laryngeal Problems

November 15 Head and Spine Injuries
- *a.* Methods of Diagnosis and Localization
- *b.* Do's and Don'ts before the patient reaches the special surgeon

U. S. Naval Hospital, Great Lakes, Illinois

October 17 Immediate and Late Care of Urinary Tract Following Injury of the Spinal Cord and Bony Structures—Dr. Vincent J. O'Conor

November 8 The Management of Acute Respiratory Obstructions—Dr. Paul H. Holinger

Camp McCoy, Wisconsin

October 18 Dermatological Diseases
Clinic with Presentation of Cases and Slides. Diagnosis and Treatment.
- *a.* The Less Common Venereal Diseases
  Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid, Yaws—Slides—Diagnosis and Treatment—Dr. G. A. Cooper

November 1 Psychiatry, Psychoneurosis, Neurocirculatory Asthenia, Malingering, etc.—Dr. Lloyd H. Ziegler

November 15 Malignancies in the Army Age Group
- *a.* Melanomata
- *b.* Teratomata
- *c.* Lymphoblastomata—Dr. Gorton Ritchie

Truax Field, Wisconsin

October 18 Virus and Rickettsial Diseases
a. Virus Diseases
b. Rickettsial Diseases—Dr. Marcos Fernan-Nunez

November 1 Peptic Ulcer and Gastritis
a. Diagnosis and Medical Care
b. Surgical Approach—Dr. Carl W. Eberbach

Note: War-Time Graduate Medical Meetings at Camp McCoy and Truax Field are arranged by the coöperating committee for Wisconsin. The members of this committee are Dr. Erwin R. Schmidt, Chairman; Dr. Elmer Sevringhaus and Dr. Francis D. Murphy.

DR. WILLIAM B. BREED
BOSTON, MASS.

OBITUARIES

DR. WILLIAM B. BREED

Dr. William Bradley Breed, Chairman of the Board of Governors and ex officio member of the Board of Regents of the American College of Physicians, died after a short illness in Boston, Mass., on August 21, 1944, four days after his 51st birthday.

Dr. Breed had been a Fellow of the College since 1928, its Governor for Massachusetts since 1934. He rendered signal service to the College. At an early meeting of the College in Boston, 1929, he was Chairman of the

Entertainment Committee; at a later meeting of the College in Boston, 1941, he was General Chairman of the Session and the success of that meeting was due to him.

Dr. Breed's devotion to the College took many forms. He had been a member of the hard-working Committee on Credentials since 1935. He was Secretary-Treasurer of the joint committee of the American College of Physicians, the American College of Surgeons and the American Medical Association, on War-Time Graduate Medical Meetings from the inception of that Committee in 1943. The noteworthy achievements of this Joint Committee represented only a part of his war-time activities. He was one of the representatives of the College on the Joint Committee on Post-War Medical Service. In addition, he was a member, and in some instances chairman, of various committees in his State and in his community.

Dr. Breed was trained in medicine at the Harvard Medical School and at the Massachusetts General Hospital. While connected with other hospitals, most of his work was done at the Massachusetts General Hospital, where he was Physician and a member of its Executive Committee. He was also Associate in Medicine at Harvard Medical School.

Dr. Breed was primarily a clinician. He belonged, perhaps, to that diminishing group of great clinical internists, as contrasted with the specialists within internal medicine, or with the medical investigators.

Dr. Breed liked people and people liked Dr. Breed. So it was inevitable that he should have a large practice, both as a practitioner and as a consultant in internal medicine. He loved life, as he loved people, medicine and music. All of his talents were at the disposal of his patients and his friends. He had a genius for friendship. The American College of Physicians has lost more than a devoted Fellow, Governor and Regent—it has lost a beloved friend.

ROGER I. LEE, M.D., F.A.C.P.,
Boston, Mass.

DR. ISAAC JUDAH SILVERMAN

Dr. Isaac Judah Silverman, F.A.C.P., Washington, D. C., died at Georgetown University Hospital, August 6, 1944, aged 56.

Dr. Silverman was born in Calcutta, India, May 3, 1888; he attended Hawthorne College, Melbourne, Australia, and graduated from the University of Melbourne Faculty of Medicine in 1911, with the degrees of M.B. and Ch.B.; he did postgraduate work at the University of Melbourne and the Washington School of Psychiatry; he practiced medicine in Australia, New Zealand, Ontario, Canada, and in St. Joseph, Mo.

Dr. Silverman was appointed to the staff of the Gallinger Municipal Hospital, Washington, D. C., in 1929, and served as Instructor in Psychiatry at George Washington University School of Medicine from 1929 to 1933. He then became a member of the teaching staff at Georgetown University School of Medicine and advanced to Clinical Professor of Psychiatry and Assistant Chief Psychiatrist at Gallinger Municipal Hospital. He was a

member of the Medical Society of the District of Columbia and the American Psychiatric Association, and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1937. He was the author of "Psychical Function of the Cerebellum" and of many articles in medical journals. His death was caused by acute myocardial infarction (posterior) and arteriosclerotic heart disease.

WALLACE M. YATER, M.D., F.A.C.P.,
Governor for the District of Columbia

DR. LESTER DOW WATSON

Dr. Lester Watson, F.A.C.P., was a casualty of this war, ending his life as he would have preferred in wartime, on active duty in the service of his country.

He was born in Dorchester, Massachusetts, on May 14, 1901, a New Englander of many generations and with forbears who, by tradition, participated in all our struggles when the need arose. He graduated from Middlebury College in 1924 with the degree of B.S.; he received his medical training at Boston University where he graduated in 1928; he served his internship at the Massachusetts Homeopathic Hospital—later called the Massachusetts Memorial—and entered practice in Milton. He maintained a continued interest in hospital work and medical teaching, and, above all, was a public spirited citizen, devoted to the welfare of his community.

He was promoted to the rank of Visiting Physician at the Massachusetts Memorial Hospitals and to instructorship at his medical school; he was a visiting physician at the Milton Hospital and Convalescent Home; he examined for the tuberculosis division of the Boston Health Department; he lent a hand in Red Cross work, civilian defense plans, and Selective Service examinations; he was a conscientious member of the Massachusetts Medical Society, the American Medical Association, and the College (Fellow, 1942); and, in addition, he was an active practitioner—a fine type of physician, alert, unselfish, competent, and beloved.

When war broke out he felt that he must play some part in it. He obtained a commission in the Public Health Service, entering on active duty in September 1943. He died on July 14, 1944, after a sudden and brief illness. He leaves his wife, Mrs. Dorthy P. Watson, and two sons.

REGINALD FITZ, M.D., F.A.C.P.,
Regent.

DR. WILLIAM STIMPSON HUBBARD

Dr. William Stimpson Hubbard, F.A.C.P., for many years an internist of Brooklyn, N. Y., died September 1, 1944, at the home of his daughter, Miss Ruth W. Hubbard, in Philadelphia, where he had lived since his retirement nine years ago.

Dr. Hubbard was born in Claremont, N. H., September 20, 1886. He attended the Holderness School for Boys at Plymouth, N. H.; received his

A.B. degree from Trinity College, Hartford, Conn., in 1888, and his M.D. degree from the Long Island College Hospital in 1894. A part of his medical training was received at the University of Michigan. For thirty years he was Assistant Attending Physician and Chief of the Medical Service, respectively, of St. John's Hospital, and a Visiting Physician to the Kings County Hospital, in Brooklyn. He had also served as Visiting Physician to the House of St. Giles the Cripple, and Consulting Physician to the John T. Mather Memorial Hospital at Port Jefferson, N. Y.

He had been a member of the Brooklyn Society of Internal Medicine, Medical Society of the County of Kings, the New York State Medical Society and the American Medical Association. He became a Fellow of the American College of Physicians in 1931 and maintained an abiding interest in the College and its activities throughout the remainder of his life. During his retirement in Philadelphia he was a frequent visitor at the College Headquarters. His was a long life of unselfish service to the profession and to the public.

DR. JAMES W. SCOTT

Dr. James W. Scott, Associate, died in the Mount Carmel Mercy Hospital, Detroit, June 25, 1944, at the age of seventy-five, of myocarditis.

Dr. Scott was born July 1, 1868, in Lancastershire, Scotland. His early training was received in Scotland, whereupon he came to America and received his medical education at the Michigan College of Medicine and Surgery, graduating in 1896. He later did post-graduate study in Glasgow and Edinburgh, Scotland. He had been a member of the Michigan State Medical Society and the American Medical Association and was an Associate of the American College of Physicians since 1920, by virtue of membership in the old American Congress on Internal Medicine, which was merged with the College in 1926, its members becoming Associates of the College.

DR. CHARLES EDWIN HOMAN, JR.

Dr. Charles Edwin Homan, Jr., F.A.C.P., Medical Director of the Ochsner Clinic, died in New Orleans on July 25, 1944, of coronary thrombosis.

Dr. Homan was born in Bibb County, Georgia, July 18, 1898. He received the Bachelor of Science degree from Mercer University in 1918, and the Doctor of Medicine degree from Johns Hopkins University in 1923; he interned at the Allegheny General Hospital from 1923 to 1924.

For several years he practiced in Chattanooga, Tennessee, where he was a member of the staffs of the Baroness Erlanger Hospital and the Pine Breeze Sanatorium, and Director of the Outpatient Department of the former institution. In 1932 he became Assistant Medical Director of the Mutual Life Insurance Company, Hartford, Connecticut. He became Medical Director of the Ochsner Clinic in January, 1943.

Dr. Homan had been a Fellow of the College since 1930. He was a

member of the Orleans Parish Medical Society, the Louisiana State Medical Society, and the American Medical Association.

EDGAR HULL, F.A.C.P.,
Governor for Louisiana

DR. LOUIS LEROY

Dr. Louis Leroy, F.A.C.P., died at his home at Memphis, Tenn., May 9, 1944. Dr. Leroy was born in Chelsea, Mass., 1874, received his B.S. at the University of Nashville and studied medicine at the University of Kentucky and at the Medico-Chirurgical College of Philadelphia, graduating from the latter in 1896.

From 1900 to 1906, he was a member of the faculty of the Vanderbilt University School of Medicine, attaining the rank of Professor of Pathology and Bacteriology. In 1906, he became Professor of Medicine at the University of Tennessee College of Medicine, an appointment which he held to the time of his death. He served at one time as President of the Tennessee State Board of Health, as Nashville City Bacteriologist and as the Tennessee State Bacteriologist. He was a member of the Memphis and Shelby County Tuberculosis Commission for many years. He was formerly Vice President of the Tennessee State Medical Association and at one time, a member of the House of Delegates of the American Medical Association. He was a member of the United States Coast Guard Auxiliary.

Dr. Leroy joined the American College of Physicians in 1920, having been sponsored by the late Dr. Lewellys Barker and the late Dr. William S. Thayer, both of Baltimore.

Aside from the regular practice of medicine, Dr. Leroy followed, almost as a hobby, the study of medico-legal medicine. He enjoyed appearing in court as an expert witness, and became very proficient in this work. However, his great hobby was the Mississippi River. He probably knew as much about the history of this great River in the vicinity of Tennessee as any one who has ever lived. He knew its peculiarities, understood its treacherous nature and kept up with its ever changing channels. His greatest pleasure was to pilot a boat on the Mississippi.

During the flood in 1937, Dr. Leroy directed the Red Cross rescue work from Cairo, Ill., to Rosedale, Miss. The fleet of boats that assisted him worked night and day and rescued hundreds of families that were shut off from escape by the rising waters.

It is, indeed, difficult to understand how Dr. Leroy found time to do so much, yet he was thorough and intense in everything he did. He was a great reader, not limiting himself to medicine alone. He was widely informed on guns, pistols, and was a student of game and wild life in the Southern States. Those who knew him well were amazed at the detailed information that he could give on almost any subject.

The South has lost a good man, a great scholar and an intelligent physician.

WILLIAM CALVERT CHANEY, M.D., F.A.C.P.,
Governor for Tennessee